# Studies towards the synthesis of new irreversible and selective reversible ligands for the kappa opioid receptor

Chauvignac, Cic

*Award date:*
2005

*Awarding institution:*
University of Bath

# STUDIES TOWARDS THE SYNTHESIS OF NEW IRREVERSIBLE AND SELECTIVE REVERSIBLE LIGANDS FOR THE KAPPA OPIOID RECEPTOR

Cédric Chauvignac

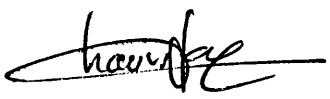
A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Pharmacy and Pharmacology

March 2005









ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

# ABSTRACT

There is considerable interest in the synthesis of κ-antagonists as therapeutic agents but also as a means of further understanding the role of the κ-opioid receptor. In the search for irreversible and selective reversible κ-opioid antagonists, it was decided to modify the structures of the two most well-known κ-antagonists, GNTI and norBNI. In particular, two main approaches have been used for the design of novel ligands; these explored the introduction of electrophilic (isothiocyanate) or lipophilic (substituted/unsubstituted benzyl) groups onto the guanidinium moiety of GNTI or at the pyrrolic nitrogen of norBNI.

In the first series of compounds, *p*-hydroxy-, *m*-hydroxy-, *p*-methoxy-, *p*-methyl- and 3,4-dichlorobenzylGNTI analogues have been prepared. Binding and functional studies of *p*-hydroxy- and *m*-hydroxy-derivatives have confirmed the results of molecular modelling studies, which had suggested that the phenolic group of the former should mimic the second phenolic group of norBNI that was previously shown to be crucial for κ-antagonist selectivity. Electrophilic ligands modelled on GNTI have also been prepared and N'-(5-isothiocyanatopentyl)GNTI has been sent for biological evaluation, while the successful synthesis of N'-(4-aminobutyl)GNTI will allow the preparation of the corresponding isothiocyanate to be achieved.

Modification of norBNI followed previous studies where the duration of action of naltrindole was extended by indolic N-benzylation. *In-vivo*, BnorBNI was a μ-agonist when administered sc and an irreversible κ-antagonist when administered icv. This led us to prepare 17,17'-di-NMe derivatives of norBNI and BnorBNI as potential mixed μ-agonist/κ-antagonist ligands. Binding and functional studies of these analogues showed that replacement of the cyclopropyl methyl groups with methyl groups led to a decrease in κ-antagonist potency and μ-agonist potency with concomitant increase in μ-agonist efficacy. We have also prepared isothiocyanates modelled on BnorBNI, with the electrophilic moiety attached directly to the benzyl group of BnorBNI or linked by a methylene spacer. At the time of submission, pharmacological evaluation of these ligands was still outstanding.

Finally, unexpected reactions with norBNI have led us to investigate whether the *p*-phthalimidobenzyl group can be used as a general protecting group for indolic and pyrrolic nitrogens. Evaluation on carbazole, tetrahydrocarbazole and an indolomorphinan has shown this is not the case.

# ACKNOWLEDGEMENTS

How could I not start this section by acknowledging the Great and Unique Stevey "McManama" Husbands? Of course, I would like to thank Steve for all the precious guidance he gave me during my project, but above all for being such a great friend, always welcoming me in his office, up for a chat and always willing to help. I am truly aware of the luck I had to spend these last three years working for such a great boss and surely one of the funniest and nicest people I've met in my life. I also would like to acknowledge John (Dr Lewis) for his good advice at some crucial points of my PhD and for the entertaining talks we had, especially when it came to sport matters.

All my gratitude goes to a few special people who made my time in Bath all the more enjoyable and help me hang in there during the difficult time: above all, Christiano Millerdonna for introducing me to Bath local population, for inviting me to some memorable parties, for organising the football sessions and camping trips (in beautiful Wedmore), for all the tips on a P&P course, etc... Also Dave and Neil for all the good vital "sessions" and nights we had clubbing and "pubbing" in Bath, Boberto Carlos for being such a permanent entertainment during these 3 years at Bath Uni, whether it was on a football pitch, on a camping trip or in a nightclub. I also particularly appreciated the company of the two wise men that are Koen and my "personal squash coach" Fabrice Jourdan; thank you for all the help and good advice for my project and during my job search.

Thank you to all the members of the Flying Boots Squad,™ with whom I have shared many enjoyable moments but also great frustration. I have also enjoyed the company of labmates Ian (whose talent for choosing the best movies was well-appreciated), Adrian, Claire, Shefali, Peter, Shi Li, Osama, Yu Xi, Mr Li, Pilan and all the other postgrads and members of staff at Bath University.

Special thanks to my family who have always ranked the financing of my studies as top of the list.

Thanks to the National Institute on Drug Abuse for funding.

# TABLE OF CONTENTS

# ABBREVIATIONS (1/2)

| | |
|---|---|
| Ar | aromatic |
| BBB | blood/brain barrier |
| BOC | *tert*-butoxycarbonyl |
| BOP | benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate |
| br | broad |
| cAMP | cyclic adenosine monophosphate |
| $CDCl_3$ | deuterated chloroform |
| $CHCl_3$ | chloroform |
| °C | degrees Celsius |
| CHO | Chinese hamster ovary |
| CPM | cyclopropyl methyl |
| CREB | cAMP response element binding protein |
| d | doublet |
| DCM | dichloromethane |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | N,N-dimethylformamide |
| DMSO | dimethylsulfoxide |
| EI | electron impact |
| EL | extracellular loop |
| equi | equivalents |
| FAB | fast atom bombardment |
| GDP | guanosine diphosphate |
| GPCR | G-protein-coupled receptor |
| GPI | guinea pig ileum |
| GTP | guanosine triphosphate |
| h | hour |
| icv | intracerebroventricularly |
| IL | intracellular loop |
| Hz | hertz |
| *J* | coupling constant |
| m | multiplet |
| M | moles per litre |
| MHz | mega hertz |

# ABBREVIATIONS (2/2)

| | |
|---|---|
| µg | microgram |
| ml | millilitres |
| mmol | millimole(s) |
| MOE | molecular operating environment |
| mol | mole(s) |
| mp | melting point |
| MS | mass spectrometry |
| MVD | mouse vas deferens |
| *m/z* | mass to charge ratio |
| NAc | nucleus accumbens |
| NIDA | National Institute on Drug Abuse |
| NMR | nuclear magnetic resonance |
| ORL | opioid receptor like |
| Ph | phenyl |
| PMB | pentamethylbenzene |
| ppm | parts per million |
| q | quartet |
| RAVE | relative activity versus endocytosis |
| $R_f$ | retention factor |
| Room T° | room temperature |
| s | singlet |
| SAR | structure/activity relationship |
| sc | subcutaneously |
| t | triplet |
| TBDMS | *tert*-butyldimethylsilyl |
| TEA | triethylamine |
| THP | tetrahydropyranyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TM | transmembrane |
| TMS | trimethylsilyl |
| UV | ultra-violet |

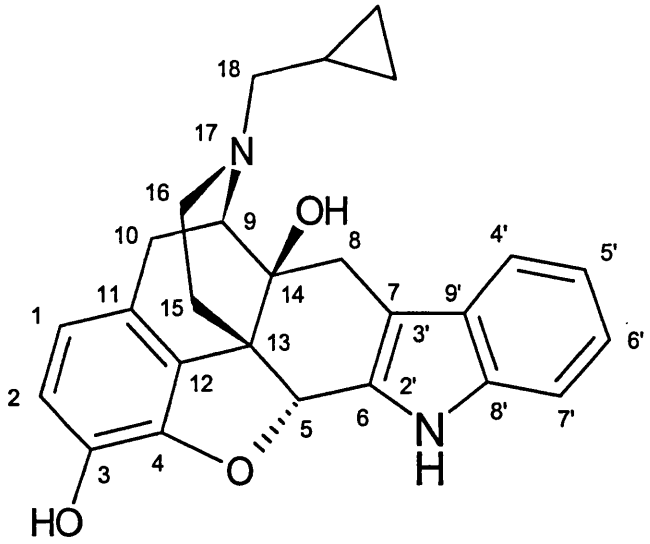
# LIST OF ILLUSTRATIVE MATERIALS (1/3)

# LIST OF ILLUSTRATIVE MATERIALS (2/3)

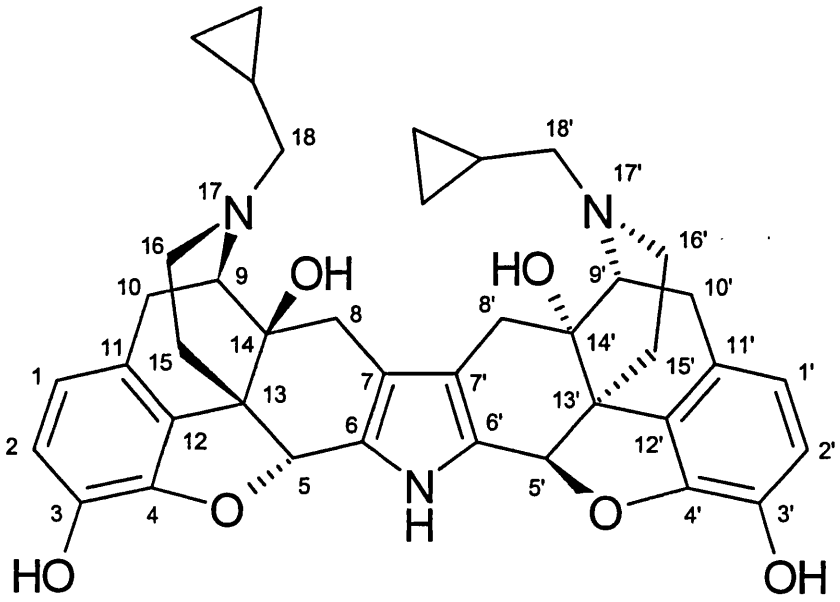
# LIST OF ILLUSTRATIVE MATERIALS (3/3)

# NUMBERING SYSTEM

Ligands based on the core of naltrindole (indolomorphinans)




Ligands based on the core of norBNI (bimorphinans)

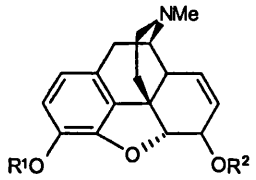


# 1. INTRODUCTION

## 1.1 Opioid receptors

Opioid research is not new in that it goes back to early centuries when the experimental use of the poppy, *Papaver somniferum*, proved to confer central analgesic relief to severe pains. However, the exotic origin of the substance together with the euphoric effects experienced upon consumption saw the use of opium drift from therapeutic background to recreational abuse. In 1803, the German pharmacist Serturner isolated morphine **(1)**, the component responsible for the analgesic and rewarding properties of opium. With the popularisation of morphine, drug addiction became increasingly associated with loss of production, death, delinquency and safer alternatives were urgently required.

In the 1920's, Gulland and Robinson revealed the structure of morphine[1] and in 1952 its total synthesis was reported.[2] Ironically, initial efforts to produce harmless analogues led to the synthesis of heroin **(2)** (the diacetyl derivative of morphine), a somewhat more addictive substance. In order to produce opioids free of addictive effects, a better knowledge of the underlying mechanisms involved in opioid activity was therefore necessary.



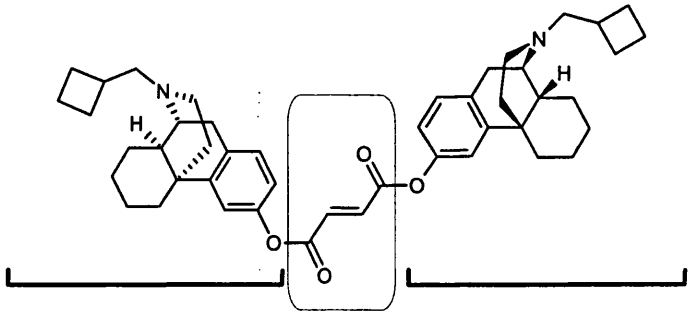

$R^1 = R^2 = H$ **1**

$R^1 = R^2 = Ac$ **2**

The existence of the opioid receptor was postulated in the 1930's by two stereochemists Beckett and Casy and later confirmed by the pioneering work of Martin *et al.* in 1976.[3,4] It is now well established that at least three different types of opioid receptors –known as "classical" types– are present within the central nervous system and peripheral sites: μ for the receptors that mediate the actions of morphine, κ for the ones that mediate the actions of the synthetic ligand ketocyclazocine and δ associated with the actions of the endogenous endorphin and enkephalin. [3,4,5] In 1992, the first opioid receptor (mouse δ) was cloned, soon followed by the cloning of the mouse μ and κ receptors in 1993,[6] before the cloning of human opioid receptors was achieved.[7,8]

The existence of subtypes within the μ, δ and κ opioid receptors has also been proposed by several research groups.[9,10,11] However, there is still a lot of debate on both the nature and existence of these subtypes,[10] as cloning of these receptors has not been achieved yet and it is increasingly believed that they could instead represent posttranslational modification of the 3 classical types.[12] Further confusion arose when additional opioid receptors such as the ε type [13,14] or opioid receptor-like (ORL) receptors were proposed. Although the latter have been shown to mediate analgesia, they fundamentally differ from opioid receptors in that they do not bind any endogenous or synthetic opioids.[15]

A revolutionary concept for the explanation of additional opioid receptors has recently emerged and relies on the organisation of opioid receptors as dimers/oligomers,[16] a process already known for other receptor systems. The existence of δ/κ heterodimers [17,18] and δ/μ heterodimers [10] has already been proposed, with however some controversy still remaining around the theory; indeed, the bivalent ligands used to prove the existence of these receptors have for long consisted of two pharmacophores linked by a bridge of 20 atom units,[16,19] a somewhat large spacer (around 22 Å) that could bind two adjacent receptors. Only recently have bivalent ligands with a reduced spacer such as compound **3** been used to probe the existence of dimeric receptors.[20]




1st pharmacophore spacer 2nd pharmacophore

**3**

However, these ligands still do not constitute irrefutable proof, as it is possible that the observed pharmacological profile stems from the mixture of monomers obtained after metabolism of the drugs. Definite evidence is therefore required but such heterodimeric structural rearrangement of opioid receptors would represent a valuable tool to account for many "odd" pharmacological behaviours that are not consistent with a "classical" monomeric model. Heterodimers should indeed exhibit

different selectivity and signal transduction pathways than monomers,[21] and this could explain, for example, why a highly selective κ-antagonist such as norBNI has been shown to antagonise the activity of highly selective δ-agonists;[17] this is illustrated in figure 1 and explained below.[19]

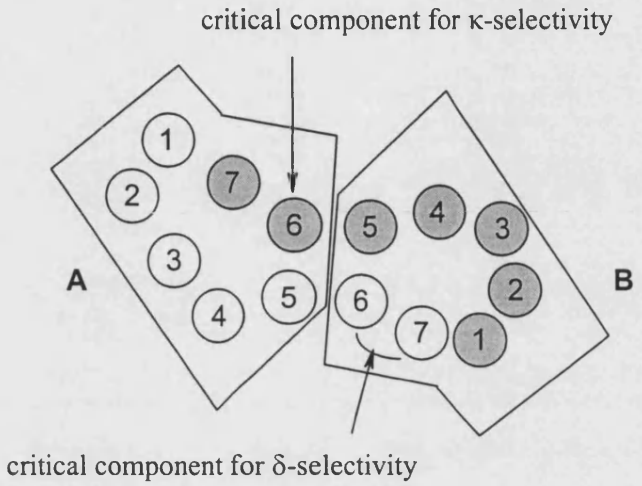



**Figure 1** Schematic model of a heterodimeric opioid receptor; the numbers represent transmembrane domains (TM) [19]

The figure 1 represents a heterodimeric receptor constituted from a κ-opioid receptor (full circles) and a δ-opioid receptor (open circles) presenting a transmembrane (TM) 5,6 interface. Let us suppose for example that the molecular features critical for κ- and δ-selectivity are contained respectively in TM 6 of the κ-receptor and extracellular loop (EL) 3 of the δ-receptor (all these terms will be described later). One might thus also envisage the heterodimeric receptor as constituted of hybrid receptors **A** and **B**. An agonist **X** selective for the δ-receptor will therefore bind to the hybrid receptor **B**. When a κ-selective antagonist **Y** binds to hybrid **A**, it produces a conformational change of both **A** and **B**; this might result in the shifting of **B** to an inactive state and subsequent antagonism of **X**.

## 1.2 The structure of opioid receptors and ligand recognition

All opioid receptors belong to the superfamily of G-protein-coupled receptors (GPCRs) and are formed with a 7-TM domain, an extracellular N-terminal and an intracellular C-terminal portions as shown on figure 2.

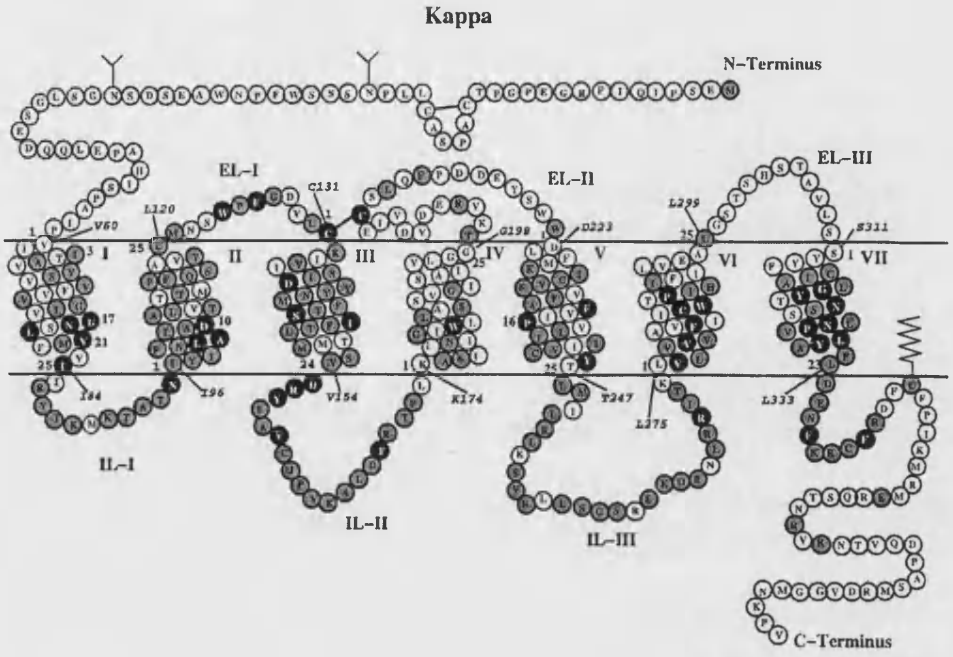



**Figure 2** Structural model of the κ-opioid receptor [19]

Studies using site directed mutagenesis and mutant opioid receptors have helped in elucidating the role of each portion of the receptor. It is now generally acknowledged that the TM domain is highly conserved between the three different opioid receptor types and is the region involved in the message recognition site (explained further) [22] whereas selectivity may be conferred by the highly divergent EL, mainly through favourable interactions between the ligands and the amino acid residues of the EL and partially by a process of exclusion (unfavourable interactions).[23,24] It is noteworthy that selectivity observed with very small ligands is still poorly understood, as such molecules are believed to bind exclusively to the TM domain of the receptor, with no interaction with the EL. The region between TM5 and TM6 –third intracellular loop (IL)– is highly conserved among the three types and is the main portion responsible for G-protein activation.[25,26]

## 1.3 Pharmacological responses

### *1.3.1 Analgesic response*

Opioid receptors are situated on the neuronal circuit responsible for pain perception (ascending sensory pathway) and modulation (descending inhibitory pathway). In response to the events experienced as painful or stressful, endogenous

opioid ligands are synthesised and released within the central nervous system; binding of these ligands to the EL and/or TM of the opioid receptors causes conformational changes of the IL that act as a switch to activate the G-protein, thereby triggering a whole series of intracellular reactions ultimately leading to analgesia (antinociception).

There is still substantial uncertainty surrounding the mechanisms evoked in G-protein activation and subsequent signaling responses, for example little is known about which conformational changes of the third IL are necessary to obtain the active state of the receptor.[24,27] The signal transduction process is however now well established and is represented in figure 3.

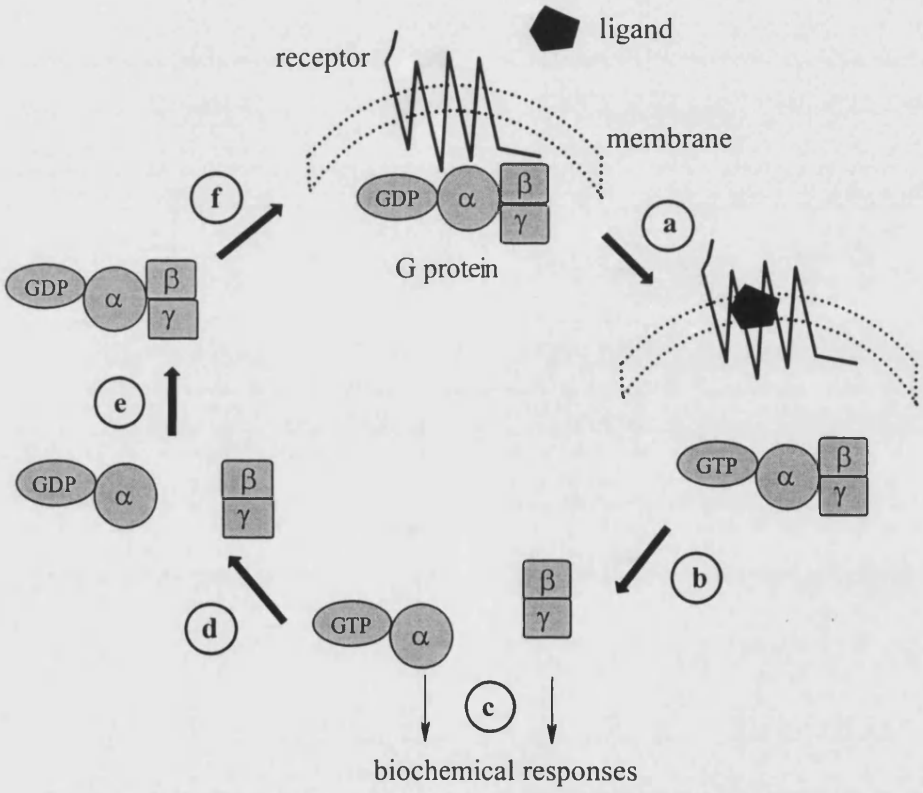



**Figure 3** Ligand binding and pharmacological responses

The G-protein coupled to all opioid receptors is heterotrimeric and composed of three different units: $G_\alpha$, $G_\beta$ and $G_\gamma$. Upon activation of the receptor, the α subunit dissociates from GDP and associates with GTP, resulting in dissociation of the G-protein from the receptor (phase a, figure 3) and in separation of the α unit from the

βγ dimer (phase b).[28] Each of these units associates with different effectors and modulates biochemical responses, namely decrease of adenylyl cyclase and cAMP, which in turn causes reduction of $Ca^{2+}$ influx and $K^+$ efflux at ion channels (phase c). This results in hyperpolarisation of the cell, reduced excitability and blunting of the "pain" signal. Hydrolysis of GTP to GDP (phase d) leads to the reassociation of the αβγ heterotrimer (phase e) and to a return to the resting state (phase f).

### *1.3.2 Side effects*

Although analgesia is a pharmacological response to activation of all three opioid receptors, each receptor type mediates a unique pattern of biological responses as shown in table 1.

| μ | κ | δ |
|---|---|---|
| analgesia | analgesia | analgesia |
| respiratory depression | diuresis | convulsions |
| constipation | sedation | constipation |
| euphoria | dysphoria | |
| urinary retention | | |
| dependence | | |

**Table 1** Pharmacological responses mediated by opioid receptors

The side effects mediated by the opioid receptors are troublesome and, in the case of acute pain, generally leave the practitioner with a dilemma: either the practitioner opts for low analgesic doses free of side effects but the pain is not adequately controlled or the pain is fully controlled but the patient experiences significant debilitating side effects.[29] Of additional and greater concern are however the side effects related to tolerance, dependence and addiction.

*1.3.3 Development of tolerance, dependence and addiction*

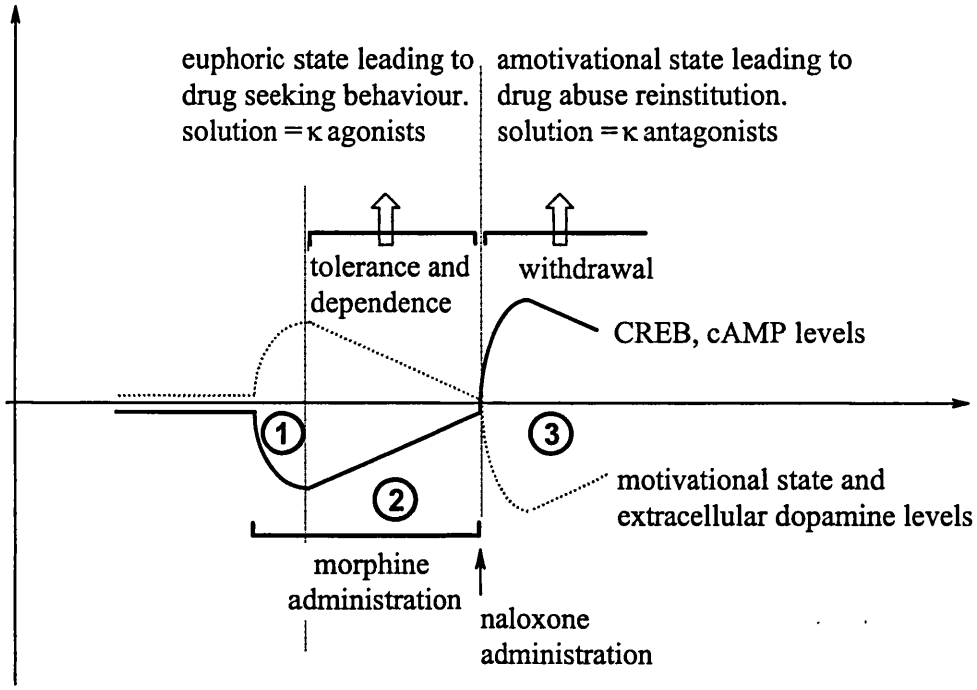
The present project has been sponsored by the National Institute on Drug Abuse from the USA and a large part of our efforts are directed towards a better management of opioid and cocaine abuse. Before emphasising the therapeutic potential of κ-selective ligands as a treatment of addictive behaviours, it seems therefore of interest to give a brief insight into the mechanisms leading to tolerance, dependence and addiction.

Agonist binding to the opioid receptor leads to immediate phosphorylation of the latter by protein kinases, which in turn triggers the recruitment of β-arrestin.[30] This protein has been shown to produce uncoupling of the G-protein from the receptor (desensitisation) and internalisation of the receptor by endocytosis.[31] The receptor can then undergo degradation or be recycled back to the surface. It was originally thought that receptor down-regulation was the cause of tolerance [32] but it has recently been proposed that receptor internalisation would in fact avoid development of tolerance by recycling the receptor back to the surface in a fully active state.[30,33] With this in mind, drugs might be ranked with a RAVE (relative activity versus endocytosis) value: drugs with a high RAVE value, that is drugs that fail to invoke rapid internalisation and recycling of the receptor (such as morphine), maintain the receptor in an active state and therefore provoke changes at downstream levels, leading to development of tolerance and dependence.

New models are increasingly focussing on the post-receptor level [34,35] and it is nowadays postulated that opiate activation of the cAMP pathway and CREB in the nucleus accumbens (NAc) represents a "mechanism of motivational tolerance and dependence",[34] resulting in addiction (see figure 4).[36] Depending on whether the addictive behaviour is motivated by the search for euphoric effects or is directed by the willingness to avoid amotivational depressing effects experienced when ceasing the drug, the use of κ-agonists or κ-antagonists appears an attractive solution to the treatment of addiction (see figure 4).

The identity of the genes which cAMP and CREB target to produce this abnormal behaviour remains to be elucidated but one early finding evokes the CREB-mediated regulation of dynorphin (the endogenous κ-agonist).[34] This is interesting since κ-agonists are known to inhibit the release of dopamine and the reinforcing and rewarding effects of morphine, heroin, alcohol [34] and cocaine [37] have been shown to be in part related to the increase of dopamine in the NAc.[38] It seems therefore possible

that CREB activation upon repeated opioid administration leads to change of dynorphin levels, which in turn modifies dopamine levels, thereby triggering anhedonia, depression and drug seeking behaviour. [34,39]




Phase (1): opioid administration (*e.g.* morphine) elicits analgesia, euphoria and other biochemical responses.

Phase (2): tolerance to euphoric effects develops, hence dose escalates to attain euphoric state = dependence;[29] since they mediate dysphoria, κ-agonists might help in reducing the euphoric effects observed in (1).

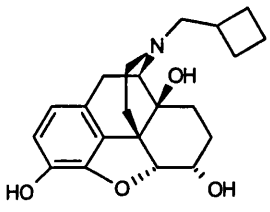
Phase (3): treatment of addiction by μ-antagonists (*e.g.* naloxone) or cessation of drug-taking precipitates withdrawal symptoms characterised by amotivational state (depression, anhedonia) and other "horrible" feelings,[40] leading to reinstatement of drug-seeking behaviour; administration of κ-antagonists might represent a solution by suppressing depression.[26,39]

**Figure 4** κ-Agonists and antagonists in the control of euphoria and dysphoria: a solution to opioid addiction? (adapted from reference 34)

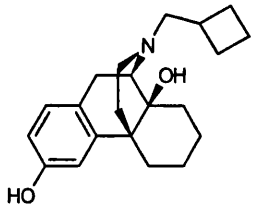
## 1.4 Significance of the κ-opioid receptor

Since opioid ligands originally disclosed were overwhelmingly μ-selective, the μ-opioid receptor has been thus far the most intensively investigated and, to the exception of the two partial agonists nalbuphine **(4)** and butorphanol **(5)**, all clinically available opioid drugs are μ-agonists.[41] However, addiction and other side effects associated with μ-agonists have led to the search for other medications.

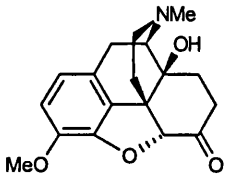
The κ-opioid receptor represents a target of particular interest in that its population is more abundant than μ- and δ-opioid receptors in humans.[42] In addition, activation of κ-opioid receptors does not elicit constipation, urinary retention, respiratory depression or euphoria [43] and has been reported to mediate less tolerance and physical dependence than observed with other opioid receptors.[44] However, psychotomimetic effects observed in clinical trials have so far impaired the therapeutic potential of κ-agonists,[45] albeit some studies have nevertheless suggested that these effects might be circumvented by slow increase in the drug dosage.[46] Special precaution is therefore required when dosing κ-agonists but further confusion arises from the lack of consistency on the statement of optimal doses; for instance, preliminary clinical studies of enadoline **(6)** showed that diuresis, dizziness, fatigue and dysphoria were mediated at doses that failed to produce analgesic effects, which led to the discontinuation of the development of the drug.[47] However, recent reassessment of enadoline has demonstrated that this κ-agonist can be safely administered at higher doses than previously used (up to 80 μg/70 kg), with psychotomimetic effects being only observed at higher doses (160 μg/70 kg).[47] It is possible that the discrepancy between these results stems from the fact that the second study was exclusively focussed on patients having drug abuse history.




**4**




**5**




**6**

### *1.4.1 Significant interest in the synthesis of κ-opioid agonists*

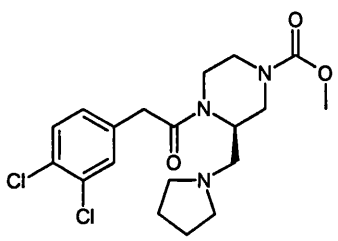
Though opioids have been historically associated with pain relief, it has become increasingly apparent that κ-agonists have a significant role to play in a wider range of clinical situations.

κ-Agonists have been reported to regulate the gastrointestinal motility in rats,[48] to lower arterial pressure and heart rate,[49] to be involved in the treatment of cerebral oedema of the focal ischemia type [50] and to stimulate food intake.[51] A few patents have recently appeared, claiming therapeutic applications of κ-agonists for the treatment of ocular and octic pains, pruritus, restless leg syndrome, irritable bladder syndrome or septicaemia.[52] Work on the $\kappa_2$-selective agonist GR89696 **(7)** showed that the $\kappa_2$-receptor subtype might offer an approach in the control of neuropathic pains (hyperalgesia, allodynia) in patients with chronic or persistent pain.[53] It should be noted however that the implication of the κ-opioid receptor in allodynia needs to be further elucidated; although the κ-antagonist norBNI has been shown to enhance this condition,[54] it is increasingly believed that allodynia could be in fact mediated through non-opioid effects of dynorphin, the endogenous κ-selective agonist.[54,55] It seems that initiation of the neuropathic pain leads to upregulation of dynorphin, thereby promoting its non-opioid pronociceptive actions, a possible critical factor for the maintenance of abnormal neuropathic pain.

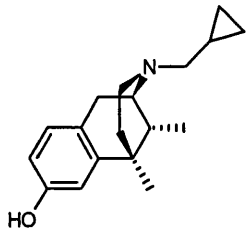
Studies using rhesus monkeys have demonstrated that κ-agonists inhibit many behavioural and neurochemical effects of cocaine related to its reinforcing properties,[56] most probably through their ability to inhibit the cocaine-induced enhancement of extracellular dopamine levels.[47,57] More recently, it has been suggested that opioids presenting a mixed κ-agonist/μ-agonist profile could represent better drug candidates for the treatment of cocaine addiction in that they should mediate fewer side effects than highly selective κ-agonists.[20,38] In particular, μ-mediated euphoric effects are expected to counterbalance κ-mediated dysphoria, resulting in dramatically enhanced treatment compliance; this should avoid repeating previous failures with κ-agonists CI-977 **(8)** and U-50488 **(9)** which were abandoned as potential treatments against cocaine abuse because of their psychotomimetic effects.[38] Also of significant interest regarding the mixed κ-agonist/μ-agonist profile is that κ-agonists have been suggested to suppress tolerance and rewarding effects experienced upon persistent activation of the μ-opioid receptor.[32]

In the particular cases of somatic and visceral pains (inflammation, abdominal surgery, pancreatitis pain), analgesia might be conferred whilst avoiding centrally-mediated side effects by either administrating small, systemically inactive doses of agonists directly into the injured tissue (useful in the case of localised pain) or by

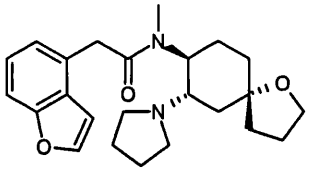
administrating peripheral agonists that have difficulties in crossing the blood/brain barrier (BBB).[43,58,59] In this perspective, κ-agonists appear as most useful as it is believed peripheral analgesia might be mediated by peripheral κ-opioid receptors.[60] Early experiments have evoked relief to capsaicin-induced hyperalgesia conferred by the κ-agonist U50,488 **(10)** in studies using rats [58] and rhesus monkeys.[61]



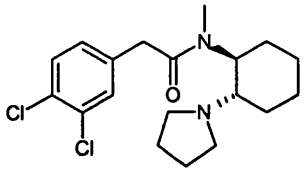

**7**




**8**




**9**




**10**

However, these constitute specific pain models and a better determination of the level at which κ-efficacy leads to dysphoria is required for more general practice. There is a fundamental need for κ-antagonists, as assessment of κ-agonist efficacy is commonly achieved through the use of antagonists as a means of immobilising the receptor reserve in a preparation, thereby placing a higher efficacy demand on agonists to produce a response.

### *1.4.2 Significant interest in the synthesis of κ-antagonists*

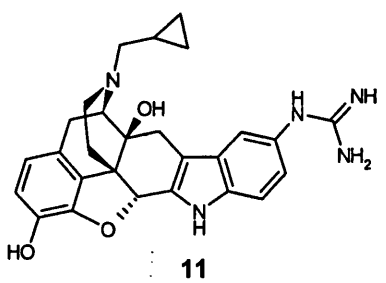
Although antagonists are mainly perceived as a tool for blocking a receptor population, κ-antagonists may also present additional pharmacological interest since they have been reported to improve recovery after traumatic brain injury [62] and might prove useful in the treatment of Parkinson's disease; it is indeed suggested that the standard κ-antagonist norBNI might prevent motor fluctuations that normally develop under levodopa therapy.[63]

In feeding studies, administration of norBNI has been shown to attenuate drinking in genetically polydipsic mice [64] and to decrease food intake induced by food

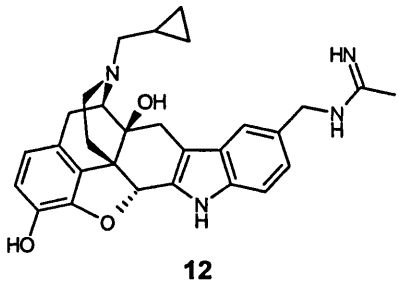
deprivation, electrically-stimulated feeding, nocturnal feeding or exposure to a high-fat diet.[51]

κ-Antagonists may also help in the treatment of depression, as GNTI **(11)**, ANTI **(12)** and norBNI **(13)** have been reported to inhibit immobility in the forced swim test,[39] an assay commonly used to study depression in rodents.[65] It is supposed that these drugs mediate antidepressant effects by blocking κ-opioid receptors that normally decrease neurotransmitter release from mesolimbic dopaminergic neurons in the NAc.[39]

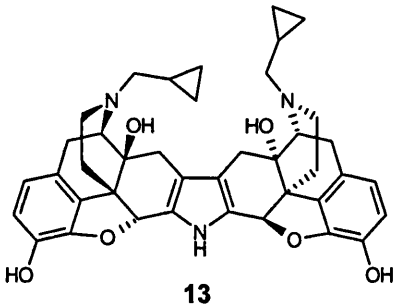
The antidepressant effects of κ-antagonists have also been investigated for the treatment of drug abuse, as dysphoria is a likely condition observed upon drug withdrawal. In post-detoxification treatment of heroin addicts, Rothman and associates have demonstrated that a combination of naltrexone (μ-antagonist) and buprenorphine (partial μ-agonist/κ-antagonist) produced a greater positive response than naltrexone alone, indicating a possible therapeutic use of κ-antagonists in the treatment of opioid addiction.[66]




**11**




**12**



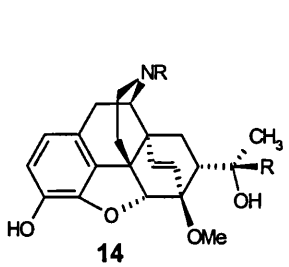

**13**

On a more general point of view, κ-antagonists might also find therapeutic use as modulatory agents to prevent the tolerance and side effects mediated by μ-selective analgesics. With this aim, peripheral antagonists could provide the best alternative since they do not antagonise centrally-mediated analgesia and one single antagonist could prevent several peripherally-mediated side effects.[67]

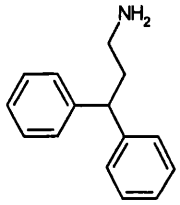
## 1.5 Opioid ligands

### *1.5.1 General remarks concerning the design of opioid ligands*

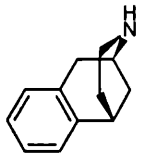
Pioneering efforts directed towards the synthesis of opioid ligands consisted of bringing slight modifications to the structure of morphine in the hope it would suppress the unwanted effects. These modifications were achieved either through the design of more complex ligands –e.g. orvinol ligands **(14)**– or *via* simplification of the morphine structure into diphenylpropylamines **(15)**, 6,7-benzomorphans (aka 2,6-methano-3-benzazocine) **(16)**, morphinans **(17)**, 4-phenylpiperidines **(18)**, 4-anilinopiperidines **(19)** and *N*-benzylpiperazines **(20)**. However, regardless of the class of ligands, there still remain strategic choices and obstacles to overcome when designing opioid ligands.



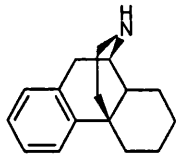

**14**



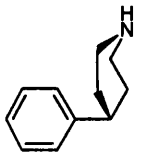

**15**



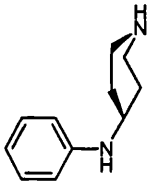

**16**



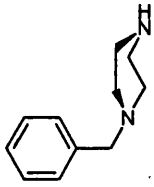

**17**




**18**




**19**



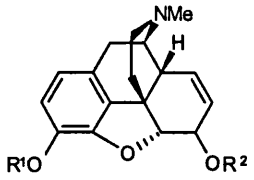

**20**

### *1.5.1.a Metabolism*

High doses of opioids required for the treatment of acute pain might result in high accumulation of metabolites in the body, and consequently in increased risks of toxicity and/or activity. Though appearing a crucial issue, metabolism has for long been disregarded when designing new ligands because of its inconsistent and unpredictable impact on the pharmacological profile of the drug. A good illustration of the problem is provided with opioid drugs containing a hydroxy group (including phenolic) such as morphine **(1)**; morphine is known to give two metabolites, namely morphine-3-glucuronide **(21)** and morphine-6-glucuronide **(22)** and the latter has been reported to possess higher potency and toxicity than morphine on an equimolar basis [68] (though interestingly the drug is being developed by the pharmaceutical company

CeNeS and is now on phase III of clinical trials). In addition, since metabolism of hydroxy groups by glucuronidation and sulfonation causes rapid excretion of the drug,[20,69] it seems attractive to develop analogues with substituted hydroxy groups.[70,71] Yet, the diacetyl derivative of morphine, heroin **(2)**, penetrates more easily into the brain because of its higher lipophilicity; it is then quickly hydrolysed into morphine, which on the whole tantamounts to rapid delivery of morphine into the brain and therefore higher abuse liability.

In the case of peptidic ligands, for which biodegradation is a fundamental issue, bioavailability might be increased by the right choice of amino acids; for example, the use of D-amino acids has proved successful with FE200041 (D-Phe-D-Phe-D-Nle-D-Arg-$NH_2$) reported as a peripheral peptidic κ-selective agonist presenting long-lasting bioavailability;[43] DAMGO (Tyr-D-Ala-Gly-MePhe-Gly-OH), the μ-selective agonist currently used in binding and functional assays, DADLE (Tyr-D-Ala-Gly-Phe-D-Leu-OH) and DPDPE (Tyr-D-Pen-Gly-Phe-D-Pen-OH), both used as δ-selective agonists in binding assays, constitute other examples.

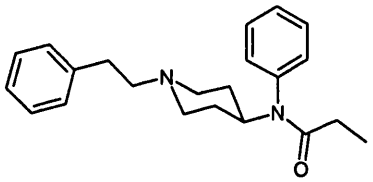



| | |
|---|---|
| $R^1 = R^2 = H$ | **1** |
| $R^1$ = Gluc, $R^2$ = Ac | **21** |
| $R^1 = R^2$ = Ac | **2** |
| $R^1$ = H, $R^2$ = Gluc | **22** |

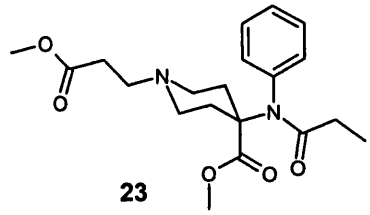
### *1.5.1.b Pharmacokinetic profile*

Although opioid analgesics almost exclusively refer so far to CNS-acting medications, there are encouraging signs that peripherally-acting drugs might prove useful for the treatment of specific pains (discussed above). As a consequence, when designing opioid ligands, medicinal chemists need to consider selectivity issues relating to the site of action. When penetrating into the brain, drugs need to cross the BBB, a very impermeable barrier to lipid-insoluble compounds: therefore, presence of extra basic groups –hence in a protonated state *in-vivo*– might be envisaged as a means to reduce accessibility through the BBB, thus increasing peripheral selectivity.[39]

In addition, since the transition between adequate pain management to pain might occur through a small variation of the drug blood concentration,[72,73] it is essential to design drugs with the right pharmacokinetics, hydrophilicity/hypophilicity ratio, rate of absorption, desired onset and duration of action. For instance, the introduction of ester functional groups in the series of fentanyl-derived ligands has proved judicious for modulating the pharmacokinetic profile of the parent drugs. The outcome was indeed better tissue solubility of the drug (remifentanil **(23)**) and rapid degradation by plasma esterases, which resulted in rapid onset and short duration of action. This prevents the drug from accumulating in the tissue, thereby alleviating dosing history issues.[73] The other striking example to illustrate the importance of pharmacokinetic properties of opioid ligands is norBNI **(13)** and this will be discussed in section 1.5.2.b.



fentanyl



**23**

*1.5.1.c Absence of a well-defined spatial arrangement of the receptor*

Although opioid receptor cloning constituted a real advance in ligand design in that binding studies using chimeras and site directed mutagenesis studies allowed the determination of specific amino acids involved in ligand recognition, it is still difficult to predict whether a ligand will target the desired key sites as no three-dimensional (3-D) crystal structure of opioid receptors is currently available. The transmembrane nature of the GPCRs has long proved challenging for crystal structure analysis and only recently has the 3-D structure of bovine rhodopsin, a member of the GPCR family, been elucidated.[74] Based on these data, 3-D computer-generated models of the three opioid receptors have appeared (see figure 5); these models rely on the assumption that the structural organisation of the transmembrane domains should be conserved within the members of the GPCR family because of high amino-acid sequence homology. Such models have since proved reliable and docking studies using these tools have been supported by site directed mutagenesis.[75]

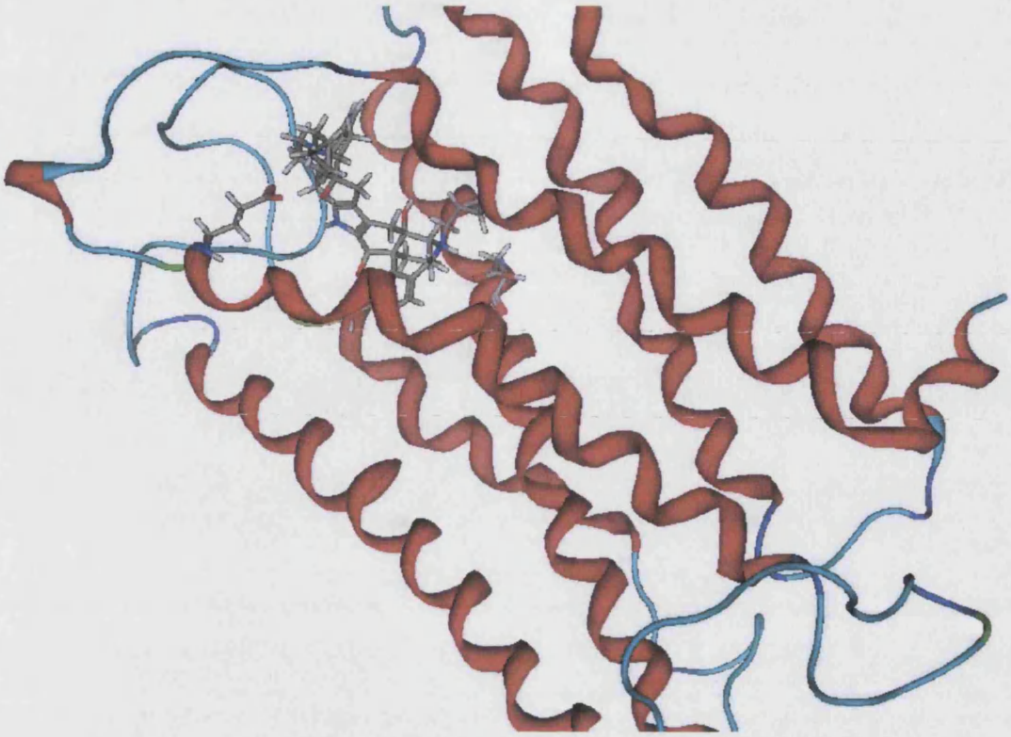


**Figure 5** Illustration of a 3-D model of the κ-opioid receptor (docked ligand is **13**)

*1.5.1.d Structure/Activity Relationship (SAR)*

The difference between an agonist and an antagonist is that an agonist shifts the receptor conformation to an active state. The switch from agonist activity to antagonist activity of opioid ligands is very subtle and can be imparted by a single change in rather complex molecules. For example, replacement of a single amino acid of peptidic ligands has been reported to change their activity (see example in section 1.5.2.a). Regarding the morphine derivatives selective for the μ-receptor, it is noteworthy that antagonist ligands are usually obtained when the nitrogen atom is substituted with an allyl or cyclopropyl methyl group whereas substitution with a methyl group leads mainly to pure agonists.[76] On the contrary, members of the phenylpiperidine class have been shown to retain their antagonist activity irrespective of the N-substituent (discussed below in section 1.5.2.b).

*1.5.2 κ-Antagonists*

*1.5.2.a Peptidic antagonists*

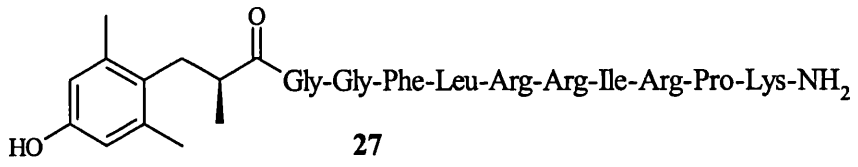
In the 1970's, isolation from brain tissue of two opioid peptides,[77] namely methionine-enkephalin (Met-enkephalin) **(24)** and leucine-enkephalin (Leu-

enkephalin) **(25)**, spurred pharmaceutical companies to synthesise peptidic ligands, as it was believed they would reveal non-addictive drugs. However, it came quickly apparent that a major challenge with peptidic opioid ligands would be enzymatic cleavage observed *in-vivo*.[44] Exchange of one or several amino acids of dynorphin A **(26)** (the endogenous ligand for the κ-receptor) led to the discovery of numerous peptidic κ-agonists with increased selectivity, stability and activity.[78] However, disclosure of peptidic selective κ-antagonists based on the core of **26** remained an elusive goal for many years until Schiller and co-workers disclosed dynantin **(27)** in 2001.[78] The design of **27** was based on the observation that a positively charged N-terminal amino group seems to be required for signal transduction but not for the binding of peptidic ligands to opioid receptors. This led Schiller and associates to replace the N-terminal $Tyr^1$ residue with 2',6'-dimethyltyrosine (Dmt), in which the terminal nitrogen was replaced with a methyl group. It is interesting to note that other examples of peptidic opioid antagonists have been reported using this technique and this might represent a general approach to switch from agonist activity to antagonist activity.[78]

$H\text{-}Tyr^1\text{-}Gly^2\text{-}Gly^3\text{-}Phe^4\text{-}Met^5(OH)$ **24**

$H\text{-}Tyr^1\text{-}Gly^2\text{-}Gly^3\text{-}Phe^4\text{-}Leu^5(OH)$ **25**

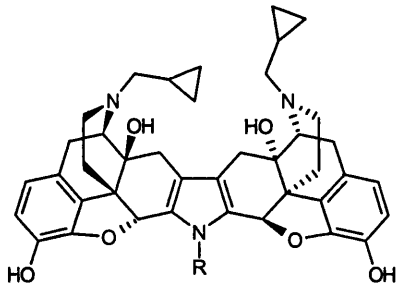
$Tyr^1\text{-}Gly^2\text{-}Gly^3\text{-}Phe^4\text{-}Leu^5\text{-}Arg^6\text{-}Arg^7\text{-}Ile^8\text{-}Arg^9\text{-}Pro^{10}\text{-}Lys^{11}\text{-}NH_2$ **26**




**27**

### *1.5.2.b Non-peptidic antagonists*

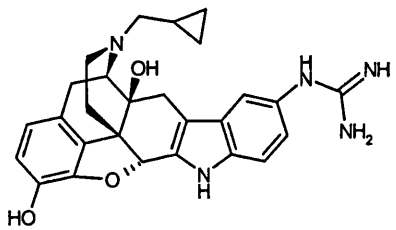
In 1987, Portoghese and co-workers reported the first two non-peptidic ligands selective towards the κ-receptor: binaltorphimine (BNI) **(28)** and norbinaltorphimine (norBNI) **(13)**.[79] To date, norBNI remains the most widely used κ-selective opioid antagonist since it shows high degree of selectivity for κ-receptors both *in-vitro* and *in-vivo*.



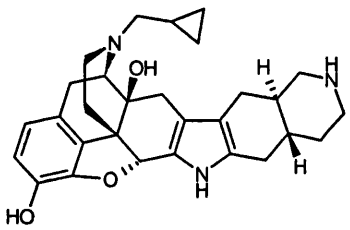
R = Me **28**

R = H **13**

NorBNI does not bind irreversibly to the κ-opioid receptor, but the slow onset and very long duration of action of **13** –up to 11 weeks in vivo [80]– are rather a consequence of the drug's bulky nature that impairs both its solubility and diffusion rates into and out of the brain.[81] The disclosure of norBNI led therefore to SAR studies in view of simplifying the drug's structure. These studies revealed that the binding of norBNI with the κ-opioid receptor follows the "message-address" concept introduced by Schwyzer: in a series of bivalent ligands, the message refers to the common molecular features that result in binding to a family of receptors whereas the part of the ligand that provides additional selectivity towards a subsite unique to one of the receptors is called the address.[82] Explicitly, Portoghese showed that only one morphinan pharmacophore (the message) and the basic nitrogen of the second morphinan (the address) were required for norBNI to maintain its activity and selectivity.[83] Of significant importance was the spatial orientation of the second basic nitrogen, as it was supposed to mimic the basic $Arg^7$ residue of dynorphin A.[19,83] With this in mind, Portoghese and colleagues developed a series of "smaller" analogues, using rigid scaffolds in order to hold the basic nitrogen in the same position as that occupied in norBNI; this ultimately led to the discovery of GNTI **(11)** [84] and the octahydroisoquinoline **29**,[85] with the former showing higher selectivity towards the κ-opioid receptor.



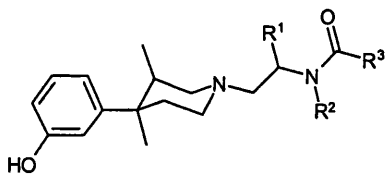
**11**



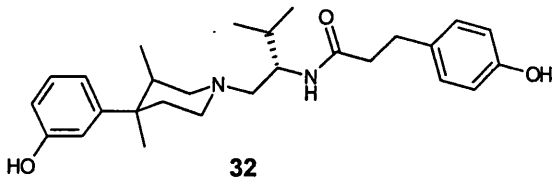
**29**

Subsequent chimera studies have supported Portoghese's intuition and have demonstrated that the second basic nitrogen interacts with an acidic residue Glu297, present in κ-receptors but not in μ- or δ-receptors, hence conferring κ-selectivity.[27,83,84] However, there is recent suggestion that the spatial orientation of the second basic nitrogen atom might not be optimal in the structure of norBNI **(13)** and its derivatives **11** and **29**.[86] Subsequent series of compounds with different spatial arrangement and basicity level conferred to the second basic nitrogen have therefore been synthesised and evaluated in pharmacological assays.[25,86,87] Although these studies further emphasized the importance of both pKa and position of the nitrogen in the selectivity and activity of the ligands,[88] no clear conclusion could be reached on the optimal design. It is noteworthy that moving the guanidine group from the 5'-position to the 6'-position resulted in a change of activity of the parent drug (from an antagonist to an agonist),[25] while moving the guanidine group from the 5'-position to the 7'-position resulted in a predictable change of selectivity (from κ to δ).[89]

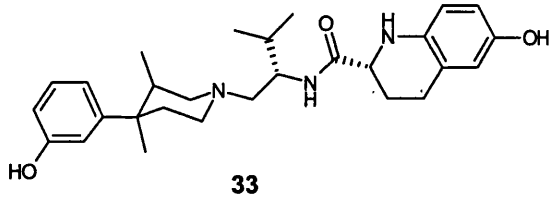
Efforts directed towards the synthesis of "small" κ-antagonists focussed initially on *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines **(30)** and 4*β*-methyl-5-(3-hydroxyphenyl)morphans **(31)**.[90,91,92,93] Although early antagonists disclosed within the former family did not exhibit κ-selectivity, their discovery nevertheless constituted a major advance in the search for κ-antagonists in that antagonist activity was retained upon modification of the N-substituent.[94] This then allowed Thomas *et al.* to use a library of compounds based on the general structure **30** and biased for opioid antagonist activity and reduced μ-affinity. This led to the discovery of the κ-selective antagonist **32** [92] and further refinement using the message/address concept culminated in the disclosure of JDTic **(33)**, as a κ-antagonist with remarkable selectivity and potency.[91]




$R^1 = R^2 = R^3$ = unspecified **30**

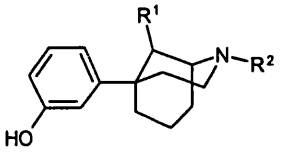



**32**

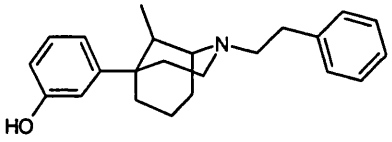



**33**

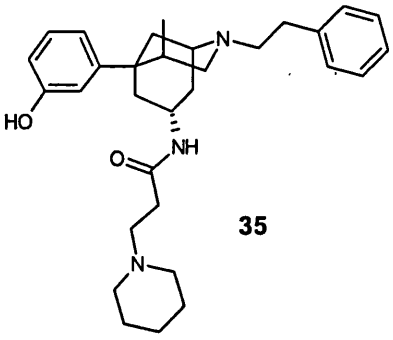
Despite structural resemblance between the *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidine family and the 5-(3-hydroxyphenyl)morphan family, the disclosure of κ-antagonists has proved more difficult in the latter case. However, the discovery of **34**, a potent antagonist at the three opioid receptors,[95] and application of the message/address concept led to **35**, the first potent and selective κ-antagonist within this family.[93]




$R^1 = R^2$ = unspecified **31**

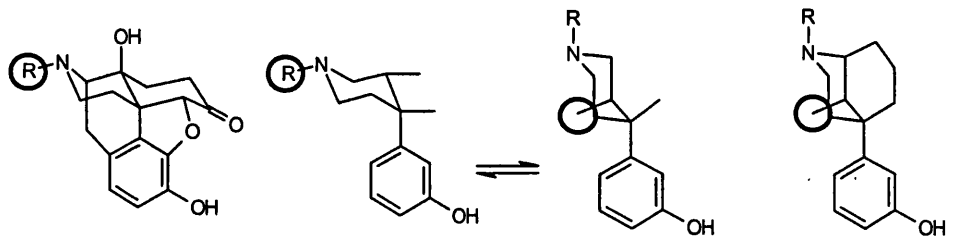



**34**




**35**

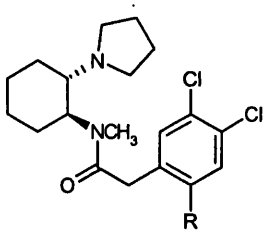
In addition, it is interesting to note that in a similar way to the *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidine family **(30)** and unlike morphine-based antagonists,[83,87] there is no evidence of efficacy being introduced when changing the N-substituent.[95] It is believed that the discrepancy in SAR behaviours stems from the fact that, upon binding of the ligands to the receptor, the N-substituent occupies different binding pockets of the receptor and thereby does not play the same role; this is illustrated on figure 6.[95] For opioid antagonists having a piperidine ring in a chair conformation and substituted with an axial 3-hydroxyphenyl group, e.g. morphinones **36** or *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines **37**, the N-substituent is postulated to be in the equatorial position and would therefore represent the trigger for antagonist activity; for opioid antagonists having a piperidine ring in a chair conformation and substituted with an equatorial 3-hydroxyphenyl group, such as 5-(3-hydroxyphenyl)morphans **38** or *trans*-(3,4)-dimethyl-4-(3-hydroxyphenyl) piperidines **39**, it is the axial 3-methyl group of **39** or the 9*β*-methyl group of **38** that are supposed to be responsible for antagonist activity; in **38** and **39**, the N-substituent confers selectivity but not activity.[95]



36 37 39 38

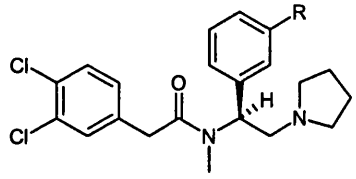
**Figure 6** Putative elements responsible for antagonist activity (circled)

κ-Antagonists are also known in the arylacetamide class of compounds, a family usually associated with κ-agonists. The rationales behind the two irreversible κ-selective ligands UPHIT **(40)** and ICI 199411 **(41)** were identical and explored the introduction of an electrophilic group onto the two κ-selective agonists U50488 **(42)** and DIPPA **(43)** with the aim of promoting irreversible binding.[96,97] However, this approach did not prove completely successful since, in both cases, irreversible antagonism is preceded by agonism. It is believed that **40** and **41** initially mimic **42** and **43**, thereby shifting the receptor to an activated state; subsequent nucleophilic attack on the isothiocyanate groups results in conformational change of the receptor and loss of activity. Such tools might be used once their initial agonism has worn off, but it can be inferred that agonist effects of **40** and **41** might alter subsequent antagonist activity. It should be noted that the pharmacological profile of both drugs is however highly debated, including among our collaborators.



R = NCS **40**

R = H **42**



R = NCS **41**

R = H **43**

## 1.6 Aim of the present project

The need for κ-antagonists as a means of further understanding the biological processes associated with the κ-opioid receptor and as a means of better characterising κ-agonists has prompted us to develop new selective antagonists and potential irreversible antagonists for the κ-opioid receptor. Since norBNI **(13)** and GNTI **(11)** are the two most prominent κ-selective antagonists thus far reported, it was decided to modify their structure with the aim of promoting covalent binding with the κ-opioid receptor or pseudo-irreversible binding. In particular, two main approaches are investigated in the present project, namely introduction of a lipophilic group (substituted/unsubstituted benzyl) or electrophilic group (isothiocyanate) onto the guanidinium group of GNTI **(11)** or at the pyrrolic nitrogen of norBNI **(13)**.

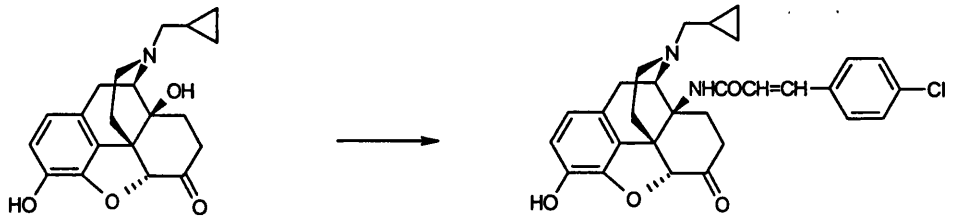
# 2. DISCUSSION

## 2.1 Benzylguanidinyl substituted ligands

### *2.1.1 Rationale*

Since GNTI **(11)** is a highly selective κ-antagonist, it represented an ideal starting point for the design of potentially irreversible κ-selective antagonists. In particular, the unsubstituted guanidinyl group appeared to provide an ideal position for further structural modification.

In 1992, Lewis and associates reported that the substitution of the 14-hydroxy group of naltrexone **(44)**, a reversible μ-selective antagonist, with a *p*-chlorocinnamoylamido group afforded C-CAM **(45)** as an irreversible μ-selective antagonist (scheme 1).[98] The irreversibility in the binding of **45** does not stem from Michael addition on the cinnamoyl group of C-CAM, as originally believed, but is likely due to very strong lipophilic interactions presumably between the styryl group of **45** and a lipophilic pocket of the μ-opioid receptor (pseudo-irreversible binding); studies with strong electron-withdrawing groups on the phenyl ring (*e.g.* $NO_2$) have indeed failed to promote covalent binding with the receptor, thus emphasising the prominent contribution of lipophilic interactions in the binding with the receptor.[99]



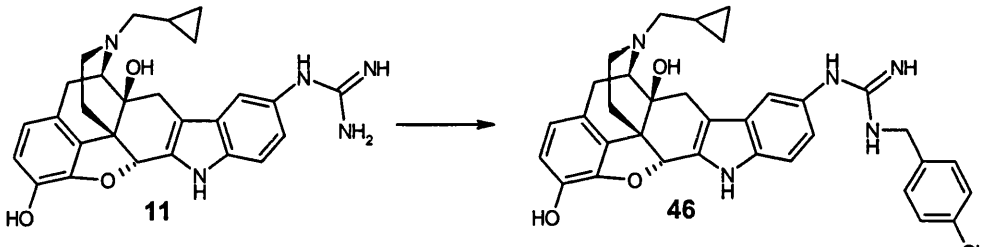

**44** — μ reversible antagonist

**45** — μ irreversible antagonist

**Scheme 1** Design of C-CAM **(45)**

Interestingly, the addition of a lipophilic group (benzyl) onto the indolic nitrogen of NTI has also been reported to result in longer duration of action of the drug (this will be further detailed in section 2.4.1.b).[100] It was thus decided to investigate the effect of similar introduction of a lipophilic group, in particular benzyl, to the reversible κ-antagonist GNTI **(11)**. In the pioneering series of benzylGNTI analogues synthesized by Dr Shannon Black, the *p*-chlorobenzylGNTI derivative **(46)** proved particularly promising since the binding in C6(δ) and CHO (κ) cells remained after washing, suggesting irreversible binding with the receptors (see scheme 2).

However, it was found in the opioid antagonist functional assay that selectivity towards the κ-receptor (37-fold κ/μ selectivity and 55-fold κ/δ selectivity) was modest compared to that exhibited by GNTI (81-fold κ/μ selectivity and 389-fold κ/δ selectivity).[101] The present project thus explores further modification of benzylGNTI in order to enhance κ-opioid receptor selectivity.

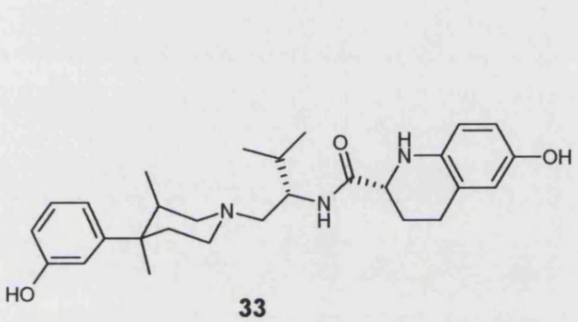



**Scheme 2** Pioneering work within our group on benzylGNTI analogues

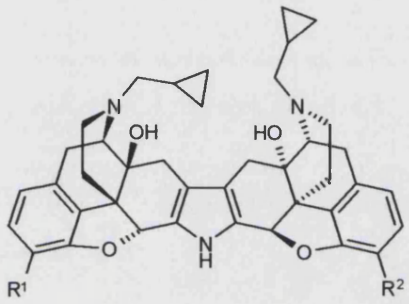
*2.1.2 Design*

As mentioned in the introduction, the phenolic group of the first pharmacophore of norBNI **(13)** has been reported to be crucial for κ-antagonist activity. To demonstrate this point, Portoghese *et al.* synthesised the 3-O,3'-O-dimethylated and 3'-O-monomethylated norBNI derivatives (**47** and **48** respectively).[102] Biological evaluation of the opioid antagonist activity showed that the dimethylated analogue **47** was inactive at all three receptors, while the monomethylated derivative **48** exhibited potency and selectivity similar to that of norBNI. It was later concluded that the second phenolic group of norBNI was not important for κ-antagonist selectivity [20,83] and this was corroborated by GNTI being a highly selective κ-antagonist.[84] However, when disclosing JDTic **(33)**, Thomas *et al.* demonstrated that both amino groups and both phenolic groups were required to maintain κ-opioid potency and selectivity.[103] Intrigued by this point, they decided to synthesise the dehydroxy analogue of norBNI **(49)**.[104] Unexpectedly, evaluation of **13** and **49** in the binding assay showed that loss of the hydroxy group had little impact on κ- and δ-affinity but entailed a 10-fold increase in μ-affinity, which resulted on the whole in no change of κ/δ selectivity but in a 10-fold decrease of κ/μ selectivity. In the functional assay, loss of the hydroxy group produced a 3.5-fold loss of κ-antagonist potency with concomitant slight increase in μ-antagonist potency and huge

decrease in δ-antagonist potency; this resulted therefore in a decrease of κ/μ selectivity and huge enhancement of κ/δ selectivity, thus demonstrating the importance of the second phenolic group in determining κ-antagonist selectivity. The discrepancy between these findings and Portoghese's earlier conclusions might be explained by the fact that Portoghese and associates used the monomethylated analogue of norBNI **(48)** to study the importance of the second phenolic group. It is possible that the oxygen atom of the second phenolic group of **13** unfavourably interacts with a group present in the lipophilic pocket of the μ-receptor. The presence of the hydrogen-bond accepting oxygen atom may therefore be important for κ-antagonist selectivity but not the presence of a hydrogen-bond donor.[104]




**33**




$R^1$ = OH, $R^2$ = OH **13** $R^1$ = OH, $R^2$ = OMe **48**
$R^1$ = OMe, $R^2$ = OMe **47** $R^1$ = OH, $R^2$ = H **49**

We have demonstrated by using the "flexible align" function implemented in MOE that, when in a low energy conformation, the phenolic group of *p*-hydroxybenzylGNTI **(50)** can be exactly overlaid on the second phenolic group of norBNI (see figure 7) and therefore could be expected to have a beneficial effect on κ-selectivity, if not affinity.

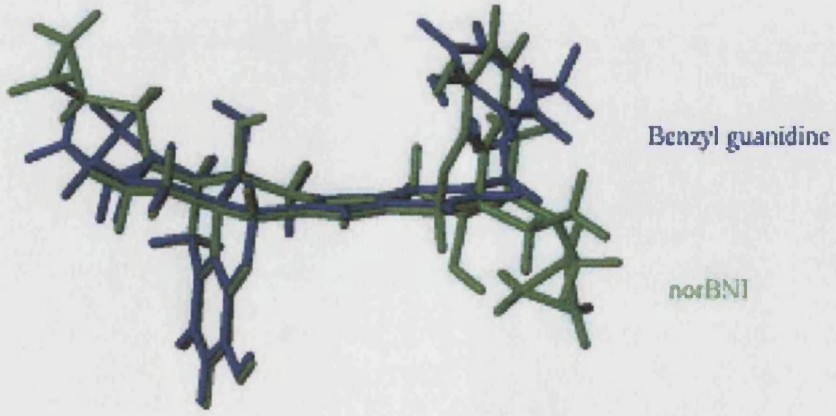
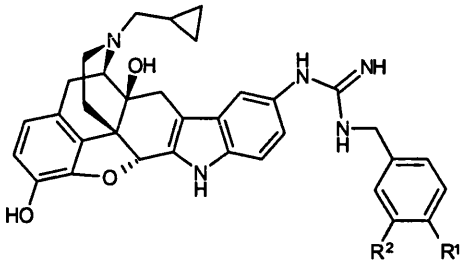



**Figure 7** Overlay of norBNI **(13)** and *p*-hydroxybenzylGNTI **(50)**

The synthesis and biological evaluation of *p*-hydroxybenzylGNTI **(50)**, *m*-hydroxybenzylGNTI **(51)** and *p*-methoxybenzylGNTI **(52)** are therefore reported in the present project. Comparison of **50** and **51** should provide information on the importance of the orientation of the hydroxyl group, while comparison of **50** and **52** will provide evidence of the importance, or not, of hydrogen-bond donating/accepting capability.



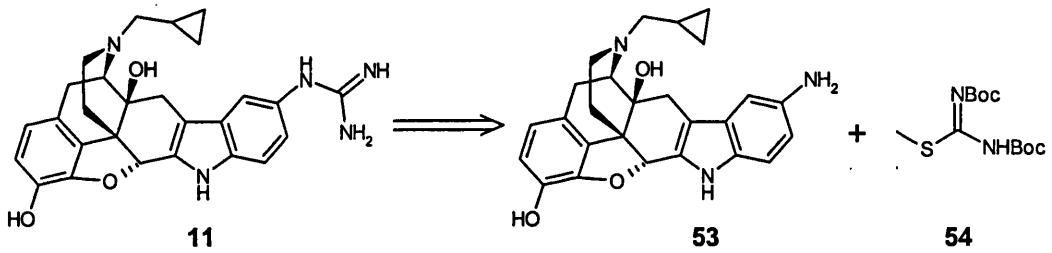

$R^1 = OH, R^2 = H$ **50**
$R^1 = H, R^2 = OH$ **51**
$R^1 = OCH_3, R^2 = H$ **52**

*2.1.3 Synthesis*

The synthesis of **50** and **51** was carried out simultaneously and will be described in section 2.1.3.a, with the synthetic route further exploited for the preparation of **52** (section 2.1.3.b).

*2.1.3.a Synthesis of p- and m-hydroxybenzylGNTI analogues (50) and (51)*

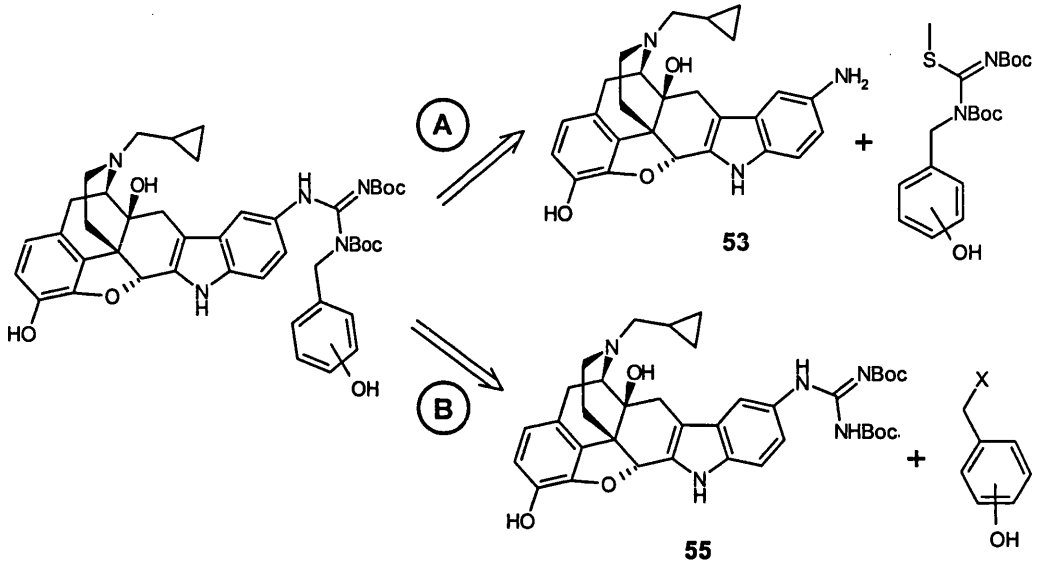
The synthesis of GNTI **(11)** is reported in the literature and involves guanidinylation of amine **53** with 1,3-bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea **(54)** (scheme 3).[84,88]




**Scheme 3** Synthetic route reported in the literature for the preparation of **11** [84,88]

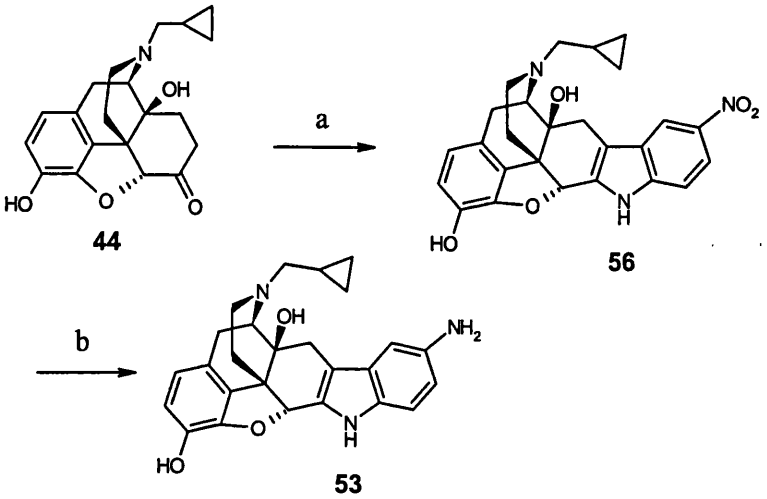
With this in mind, two different approaches might be envisaged for the synthesis of **50** and **51**, namely guanidinylation of **53** with substituted guanidinylating agents (path A) or direct alkylation of **11** (path B) as shown in scheme 4.[105] Since the latter method would require protection and deprotection of the hydroxy groups of **55**,

it was decided to synthesise **50** and **51** *via* guanidinylation of **53** with appropriately N-substituted derivatives of **54**.




**Scheme 4** Two possible synthetic approaches for the preparation of **50** and **51**

The method employed by Portoghese and associates for the preparation of amine **53** involved a Fisher indole reaction between naltrexone hydrochloride **(44)** and 4-nitrophenylhydrazine, followed by reduction of the nitro group with Raney nickel and hydrazine hydrate (see scheme 5).[88]




(a) 1.1 equi. 4-nitrophenylhydrazine, AcOH/conc. HCl, 110°C, 7 days;
(b) Raney Ni/7.7 equi. $NH_2NH_2.xH_2O$, EtOH, 2 hrs, room T°

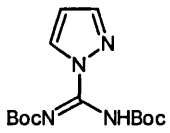
**Scheme 5** Preparation of amine **53** reported in the literature [88]

Portoghese and co-workers reported that very harsh conditions were required for the first step because of the strong electron-withdrawing effect of the nitro group on phenylhydrazine; stirring the materials for 7 days at 110°C in a mixture of acetic acid/conc. HCl thus afforded 5'-nitronaltrindole **(56)** in modest yield (43%).

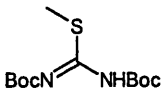
However, earlier work within our group had suggested that a shorter reaction time, a less tedious workup and a better yield could be obtained when the first step was carried out in ethanol/conc. HCl (50/50) under reflux.[106] Modifications had also been reported for subsequent reduction of the nitro group into the corresponding amine, as Raney nickel-catalysed transfer hydrogenation with cyclohexene was found preferable.[106] While the modified first step proceeded relatively well during this current study (26 % yield), the reduction of **56** to **53** using Raney Ni/cyclohexene transfer hydrogenation could not be repeated. Hydrogenation, using Raney Nickel or palladium as catalysts under an atmospheric pressure of hydrogen, also proved unsuccessful. Pd-catalytic hydrogenation, increasing the hydrogen pressure to 5 bars, gave somewhat better results, as the desired product was obtained in 31% yield. It was then decided to reproduce Portoghese's method (Raney nickel/hydrazine hydrate transfer hydrogenation),[88] which afforded the amine in 47% yield (*vs* 69% reported in the literature). Reduction using iron(II) sulfate heptahydrate/$NH_4OH$ was also attempted to see if this would allow a more efficient preparation of **53**, as this method had been satisfactorily employed within our group for the reduction of aromatic nitro groups;[107] indeed, stirring morphinan **56** and 9 equivalents of iron(II) sulfate heptahydrate at 80°C for 3 hours in a mixture of methanol/$H_2O$/conc. $NH_4OH$ afforded **53** in 56 % yield.

As noted earlier, the synthetic approach used in the present project for the preparation of **50** and **51** required the synthesis of suitable guanidinylating agents. Guanidines are generally commercially synthesised *via* the nucleophilic displacement of methyl mercaptan from S-methylisothiouronium salts by amines.[108] However, since methyl mercaptan is a highly smelly noxious gas, such a procedure requires subsequent transformation of the byproduct. The synthesis of guanidines has also been achieved by reaction of ammonia derivatives with cyanamides,[109,110] chloroformamidines,[111] aminoiminomethanesulfonic acids [112] or carbodiimides [108] but these procedures generally involve corrosive, moisture-sensitive starting materials and require high temperatures. More recently, guanidinylation employing protected

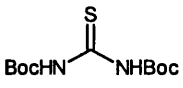
guanidinylating agents, such as pyrazole carboxamidine **57** or thiourea derivatives **54** and **58**, in presence of Mukaiyama's reagent **(59)** or a thiophile (such as mercury, copper or lead salts) [113,114] have emerged and this proved more attractive to us as the desired guanidinylating agents could be prepared by direct N-alkylation of these. Such a procedure was also employed by Portoghese and colleagues for the disclosure of GNTI **(11)**, with mercury(II) chloride being used as the catalyst for the coupling of **54** with **53**.[84,88] Although it is generally agreed that mercury forms a complex with the sulfur atom, resulting in activation of the carbon atom towards nucleophilic attack by the amine, it is not clear however whether the reaction proceeds *via* formation of a tetrahedral intermediate [115] or a carbodiimide intermediate.[116]



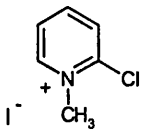

**57**




**54**



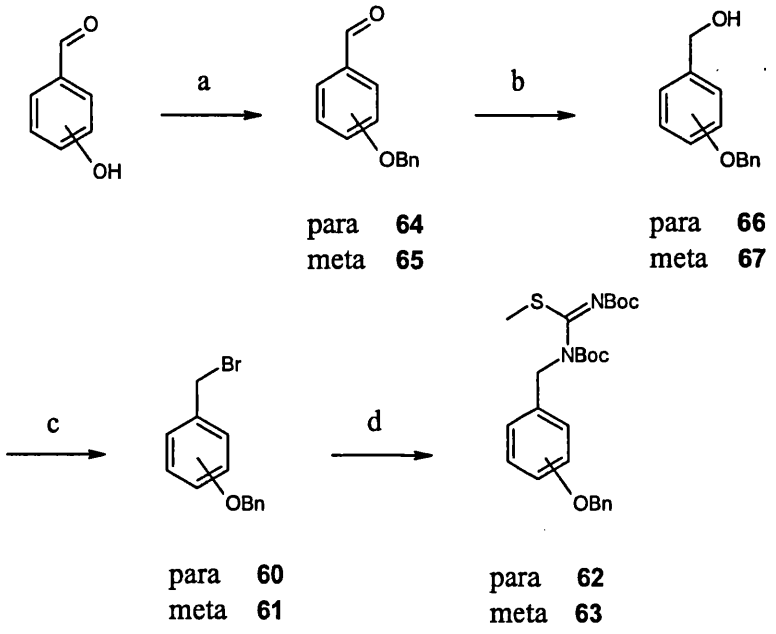

**58**




**59**

As N-benzylation of **54** with benzyl bromide derivatives **60** and **61** required the use of sodium hydride, the synthesis of guanidinylating agents **62** and **63** started with the protection of the hydroxy group of 3- and 4-hydroxybenzaldehydes (see scheme 6). Three protecting groups were initially investigated, namely benzyl, O-tetrahydropyranyl and trityl, but it appeared very early in the synthesis that the use of the benzyl group was the most promising. Benzyl-protection of 3- and 4-hydroxybenzaldehydes was achieved following the procedure used by Nicolaou *et al.*, [117] which quantitatively afforded **64** and **65** that were subsequently reduced with sodium borohydride into the corresponding alcohols **66** and **67** (93% and 84% respectively). The latter were then converted into their bromide derivatives **60** and **61** according to a general procedure reported by Lange *et al.* for the conversion of alcohols into alkyl iodides;[118] this procedure involved forming iodotriphenylphosphonium iodide salt before subsequent reaction with 0.83 equivalent of alcohol in the presence of one equivalent of imidazole; in our case, iodotriphenylphosphonium iodide was replaced by the bromide salt. Deprotonation of 1,3-bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea **(54)** with 1.2 equivalents of sodium hydride and subsequent nucleophilic attack on 1.1 equivalents of **60** and **61**,

using a similar procedure to that previously reported within our group,[106] afforded the guanidinylating agents **62** and **63** in 62% and 54% yields respectively.

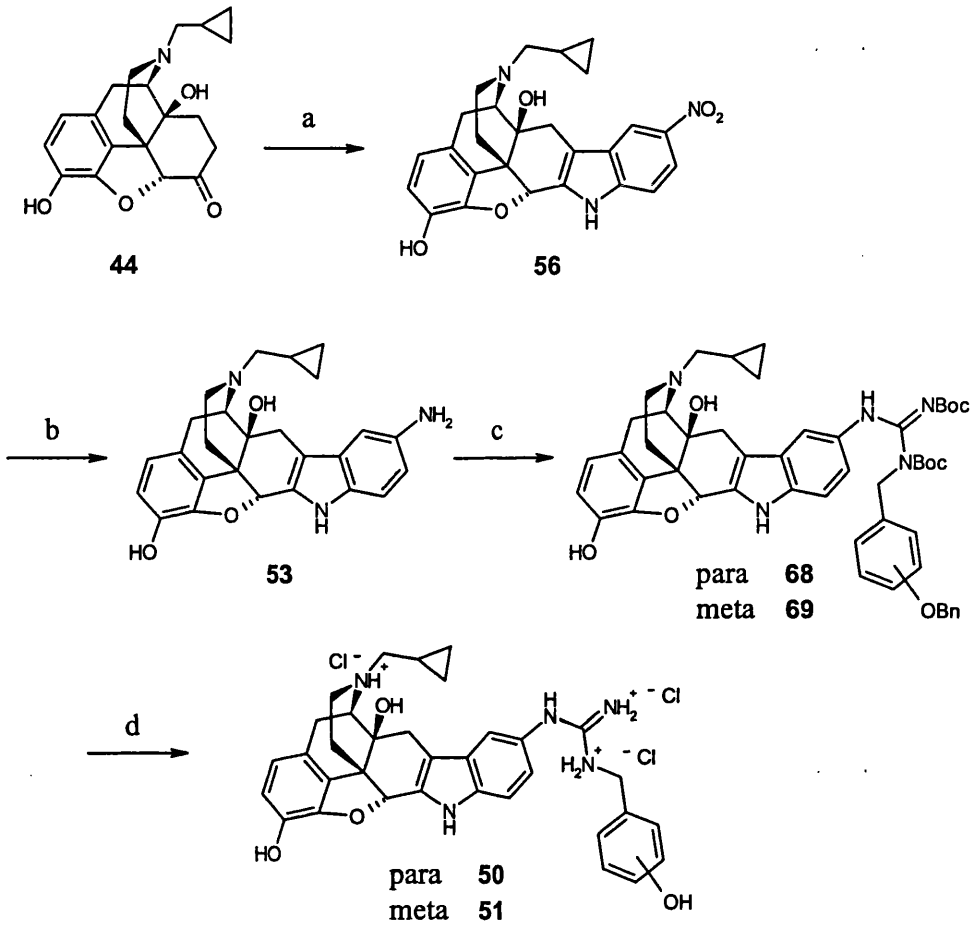



(a) 1.5 equi. $K_2CO_3$, 1 equi. BnBr, DMF, overnight, room T°; (b) 0.5 equi. $NaBH_4$, dry THF, overnight, room T°; (c) 1.2 equi. $PPh_3$, 1.2 equi. imidazole, 1.2 equi. $Br_2$, dry DCM, overnight, room T°; (d) 0.9 equi. **54**, 1.1 equi. NaH, dry DMF, 14 hrs, room T°

**Scheme 6** Preparation of guanidinylating agents **62** and **63**

Coupling of **53** with **62** and **63** was achieved following an analogous $HgCl_2$-promoted guanidinylation procedure to that reported in the literature, namely using 0.56 equivalent of mercury(II) chloride and 1.0 equivalent of both triethylamine and **53**.[84] However, since initial attempts showed that some unreacted amine **53** was still present at the end of the reaction, we eventually decided to increase the number of equivalents of mercury(II) chloride, triethylamine and guanidinylating agent (1.5, 2.0 and 2.0 equivalents respectively) (scheme 7). Simultaneous removal of the BOC and benzyl protecting groups of **68** and **69** was then attempted using a large excess of trifluoroacetic acid but this afforded products still bearing the benzyl protecting group. Since it was reported in the literature that debenzylation with TFA might be improved by adding a strong nucleophile (thioanisole) or a benzylic cation scavenger (pentamethylbenzene),[119,120] the benzyl-protected morphinans were stirred overnight

at 40°C in TFA with 20 equivalents of thioanisole, but this gave only unreacted materials. However, simultaneous benzyl and BOC deprotection was eventually achieved stirring **68** and **69** overnight in a mixture of conc. HCl/MeOH (50/50) at 80°C, which afforded the target compounds **50** and **51** in quantitative yields.



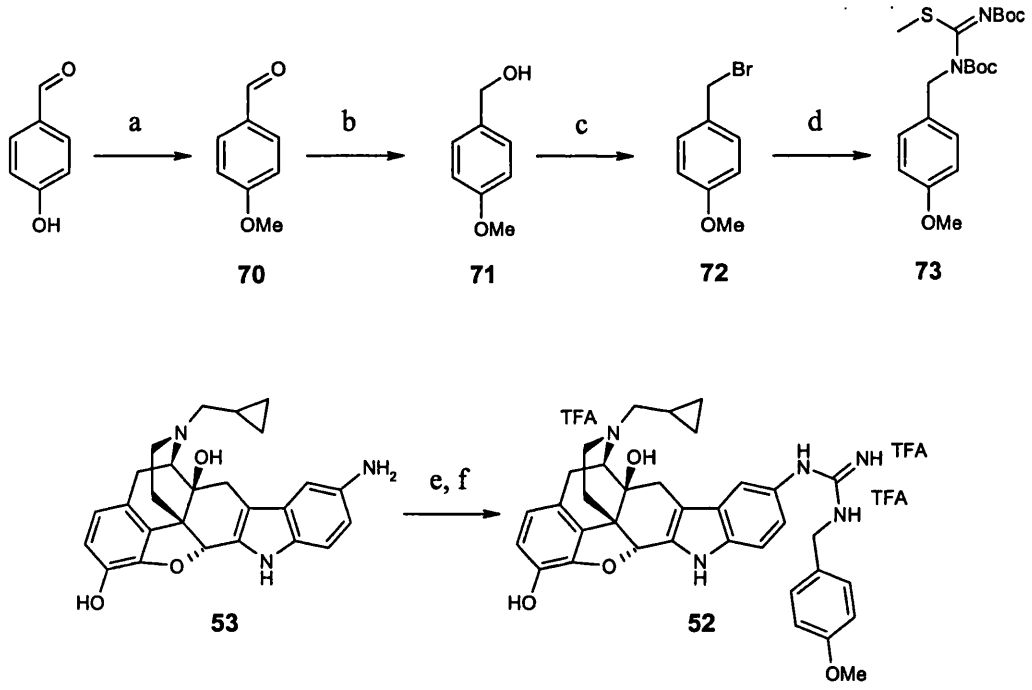

(a) 1.2 equi. 4-nitrophenylhydrazine, EtOH/conc. HCl (50/50), 24 hrs, reflux; (b) 9 equi. $FeSO_4.7H_2O$, $MeOH/H_2O/NH_4OH$, 3 hrs, 80°C; (c) 1.5 equi. $HgCl_2$, 2.0 equi. **62** or **63**, 2.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C; (d) conc. HCl/ MeOH (50/50), overnight, 80°C

**Scheme 7** Synthetic approach used for the preparation of compounds **50** and **51**

### *2.1.3.b Synthesis of p-methoxybenzylGNTI (52)*

The synthetic pathway described in section 2.1.3.a was further employed for the preparation of **52**. 4-Hydroxybenzaldehyde was reacted with 1 equivalent of

methyl iodide and 1.5 equivalents of potassium carbonate in DMF, which led to the methoxy derivative **70** in 92% yield (scheme 8). **70** was quantitatively reduced with sodium borohydride to the corresponding alcohol **71** before conversion into 4-methoxybenzyl bromide **(72)**, using the same conditions as described above for **60** and **61**. It is noteworthy that **72** could not be purified by column chromatography because of decomposition and was subsequently used without any purification. Reaction of **72** with **54** in presence of sodium hydride led to the guanidinylating agent **73** (49% yield) that was in turn coupled with **53** using the same mercury(II) chloride-promoted guanidinylation as used for the preparation of **68** and **69**. This afforded a mixture containing the desired di-BOC-protected morphinan **74** and its mono-BOC-protected analogue. Deprotection of the mixture with a large excess of TFA afforded cleanly and quantitatively the target compound **52** (see scheme 8).




(a) 1.5 equi. $K_2CO_3$, 1.0 equi. $CH_3I$, DMF, overnight, room T°; (b) 0.5 equi. $NaBH_4$, dry THF, overnight, room T°; (c) 1.2 equi. $PPh_3$, 1.2 equi. imidazole, 1.2 equi. $Br_2$, dry DCM, overnight, room T°; (d) 0.9 equi. **54**, 1.8 equi. NaH, dry DMF, 14 hrs, room T°; (e) 1.65 equi. $HgCl_2$, 2.0 equi. **73**, 2.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C; (d) DCM/TFA, overnight, room T°

**Scheme 8** Synthetic route used for the preparation of *p*-methoxybenzylGNTI **(52)**

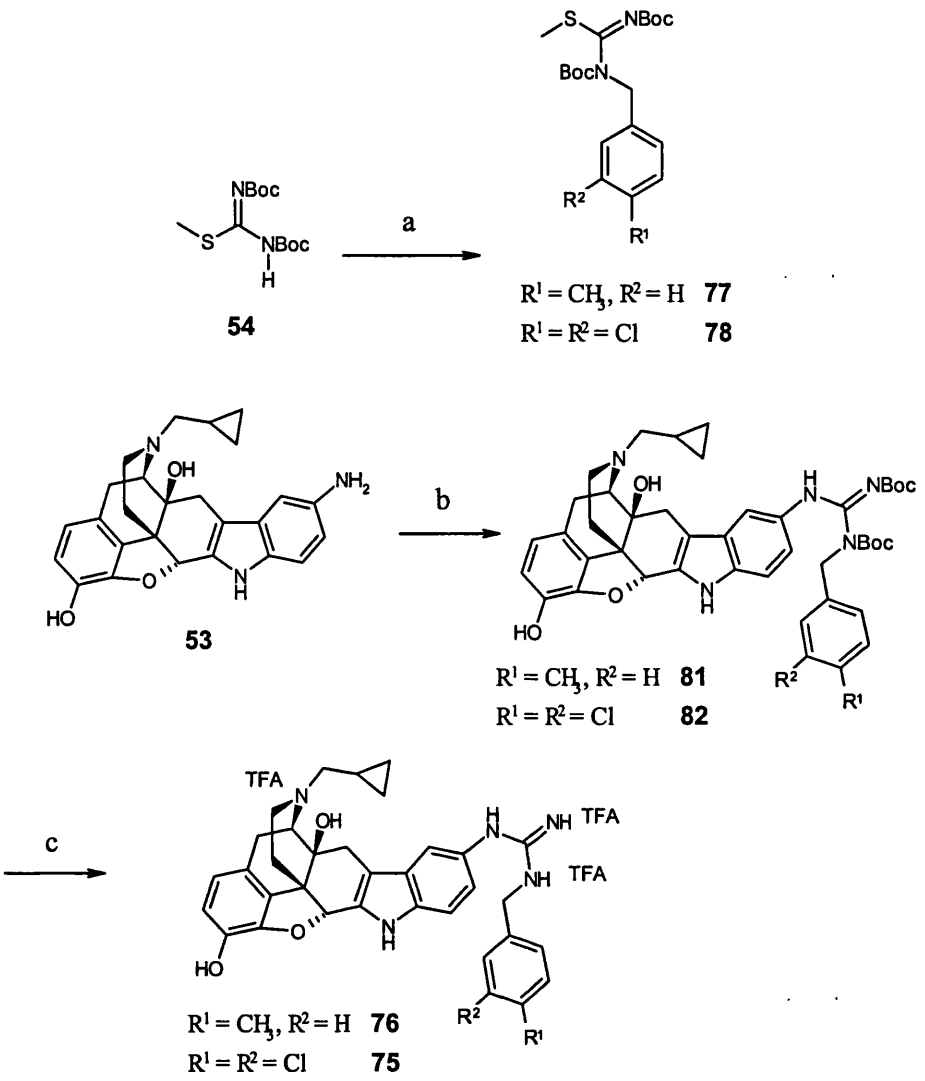
## 2.2 Further work with benzylGNTI derivatives

### *2.2.1 Rationale*

Still intrigued by the results reported by Thomas *et al.* relating to the contribution of the second phenolic group towards the binding of norBNI [104] and in our effort to develop antagonists with increased κ-opioid receptor selectivity and activity, we decided to further study the interaction between the benzylic group of benzylGNTI analogues and the lipophilic pocket of the κ-opioid receptor. A Topliss approach was thus implemented in order to investigate which physicochemical parameters of the substituent on the phenyl ring are optimal for κ-antagonist potency and selectivity. The Topliss method requires the synthesis and biological evaluation of a first series of derivatives, namely *p*-chloro, 3,4-dichloro, *p*-methyl, *p*-methoxy and unsubstituted benzyl analogues; according to the rank order of potency of these compounds, one can predict which type of substitution on the phenyl ring is optimal for activity.[121] As Dr Shannon Black had already synthesised *p*-chlorobenzylGNTI and benzylGNTI,[106] it was decided to prepare and evaluate 3,4-dichlorobenzylGNTI **(75)** and *p*-methylbenzylGNTI **(76)** (see scheme 9).

### *2.2.2 Synthesis*

The preparation of **76** and **75** was achieved using a similar synthetic strategy as used in section 2.1 and started with the synthesis of guanidinylating agents **77** and **78**. 1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea **(54)** was thus deprotonated with 1.1 equivalents of sodium hydride in presence of 0.1 equivalent of 15-crown-5; the corresponding base was subsequently reacted with commercially available 4-methylbenzyl bromide **(79)** or 3,4-dichlorobenzyl chloride **(80)**, stirring the mixture overnight at 70°C, which afforded the desired products **77** and **78** in 74% and 47% yields respectively (see scheme 9). Subsequent $HgCl_2$-promoted guanidinylation of amine **53** with **77** and **78**, using the procedure described in section 2.1, led to **81** and **82** in 68% and 74% yields respectively. It is noteworthy that both **81** and **82** were isolated as a mixture of mono- and di-BOC protected morphinans. Finally, deprotection of the morphinans (mixture of mono- and di-BOC protected derivatives) was accomplished stirring the compounds overnight at room temperature in a large excess of TFA, which led cleanly to the targets **76** and **75**.




(a) 1.1 equi. NaH, 0.1 equi. 15-crown-5, 1.2 equi. **79** or **80**, dry DMF, 14 hrs, 70°C;
(b) 1.5 equi. $HgCl_2$, 2.0 equi. **77** or **78**, 2.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C;
(c) DCM/TFA, overnight, room T°

**Scheme 9** Synthetic approach used for the preparation of **75** and **76**

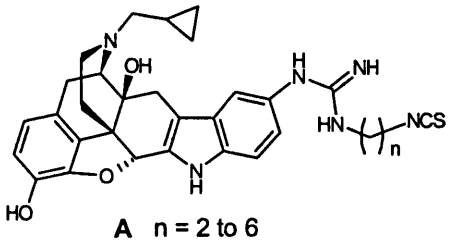
## 2.3 Irreversible guanidinyl substituted ligands

### *2.3.1 Design*

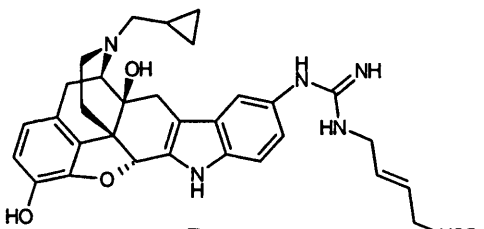
We have explored in sections 2.1 and 2.2 the possibility of promoting irreversible binding with the receptor *via* additional lipophilic interactions. This resulted in benzylGNTI analogues exhibiting pseudo-irreversible binding with the κ-receptor (see section 2.1.1). During the present project, the possibility of eliciting

covalent binding between GNTI-derived ligands and the κ-opioid receptor was also investigated.

With that aim, it was decided to substitute the guanidinium group of GNTI so as to orientate an electrophilic group in close proximity to a putative nucleophile near or at the active site of the κ-opioid receptor. The use of a wide range of electrophiles has been reported in the literature for promoting covalent binding with opioid receptors, including nitrogen mustard,[122] Michael acceptor [123] and disulfide compounds.[124] However, the isothiocyanate group appeared more attractive to us because of its reactivity profile and fairly small size, the latter generally resulting in little modification in the selectivity of the parent ligand. Isothiocyanates are known to react preferentially with amino and sulfhydryl groups while reacting slowly with water and hydroxyl functions, hence limiting non-specific binding. It was therefore decided to substitute the guanidinium group of GNTI with a series of side chains of different length terminating with an isothiocyanate group (targets of type **A** or **B**).




**A** n = 2 to 6




**B**

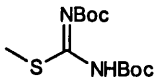
*2.3.2 Synthesis*

Although the synthesis of isothiocyanates *via* nucleophilic attack of thiocyanate ions on acyl halides,[125] alkyl halides [126] or aryl diazonium compounds [127] is reported in the literature, these methods did not appear most attractive to us as S-alkylation is also generally observed. We instead sought to prepare the targeted isothiocyanates *via* the corresponding primary amino precursors, using one of several reagents reported in the literature, including carbon disulfide in combination with BOP [128] or dicyclohexylcarbodiimide,[129] thiophosgene,[130] or di-2-pyridyl thionocarbonate.[131]

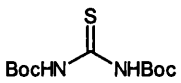
With this in mind, it was proposed to prepare the target compounds according to the same approach as used in sections 2.1 and 2.2, but using guanidinylating agents bearing a side chain terminating with a protected amino group or a moiety that could be easily transformed into an amino group.

*2.3.2.a Synthesis with guanidinylating agents bearing a terminal BOC-protected amino group*

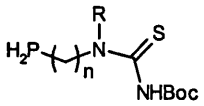
Although coupling of amine **53** with derivatives of **54** had proved relatively successful (from 30 to 74% yield, see sections 2.1 and 2.2), we decided to prepare guanidinylating agents modelled on **58** since they have been reported to give best results for the guanidinylation of sterically hindered amines;[113] for our purpose, guanidinylating agents would therefore be reagents of type **C**. Although it is reported in the literature that the presence of one proton on each of the nitrogen atoms of **58** is required for the guanidinylation to succeed, [116] suggesting that the reaction proceeds *via* the formation of a carbodiimide intermediate, preliminary results within our group with N,N'-disubstituted derivatives of **58** have shown this is not a necessary condition, which suggests the reaction might also evolve *via* a tetrahedral intermediate.[106] It is noteworthy that the BOC groups not only play the role of protecting groups but also facilitate the guanidinylating step, a consequence of their electron-withdrawing properties; thus, unprotected N,N'-dialkyl substituted thioureas have been reported not to undergo guanidinylation while di-BOC-protected thioureas have been shown to react more swiftly than mono-BOC derivatives.[116] Again however, preliminary findings within our group tended to be in disagreement with that stated in the literature, as coupling of mono-BOC protected thioureas with amine **53** had been found to proceed with great facility.[106]




**54**



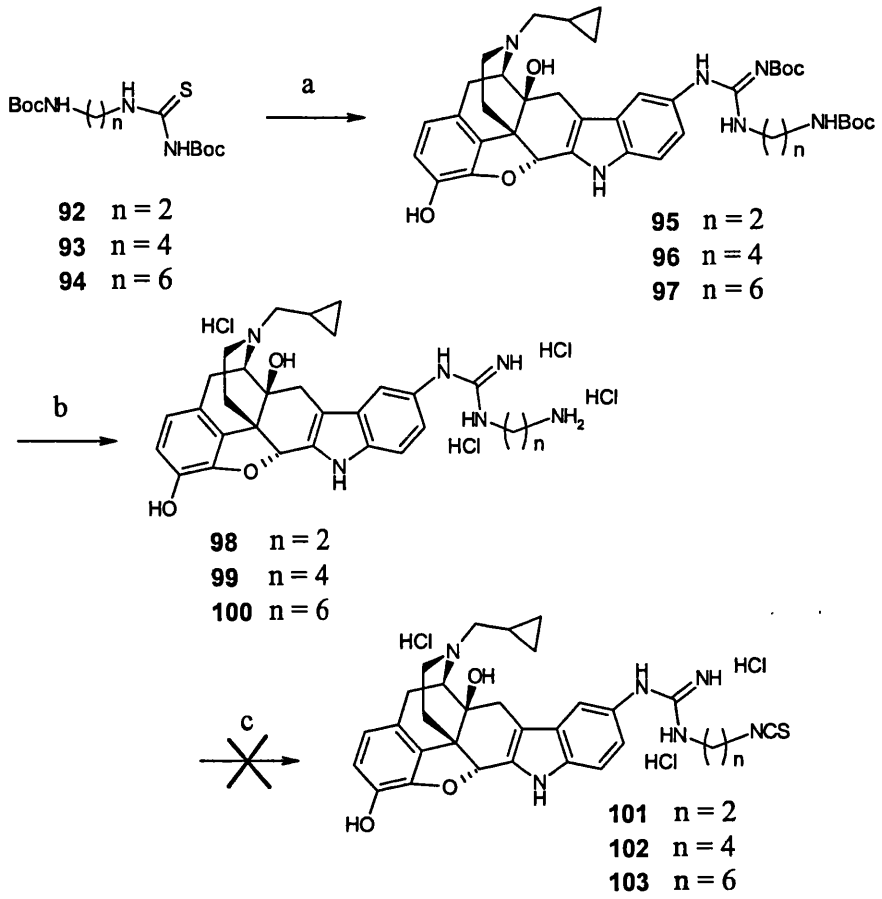

**58**




**C**

P= protected amine or amino precursor
R= H or BOC

Since it was intended to utilise BOC protecting groups on the nitrogens of the thiourea moiety, it seemed particularly attractive to use a BOC group for the protection of the terminal amino group of agents **C** (P = NHBoc) with the view of subsequently removing all protecting groups in one single step (see scheme 10).

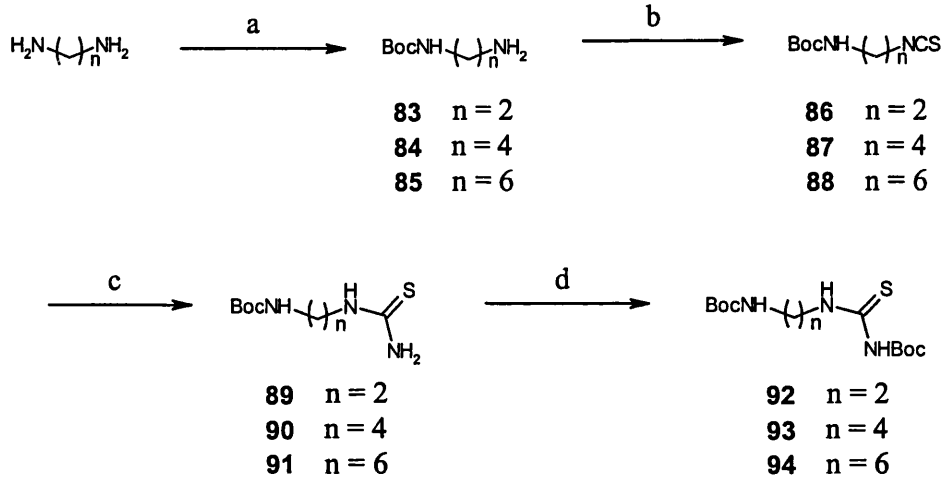



(a) 0.75 equi. $HgCl_2$, 0.5 equi. **53**, 1.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C; (b) conc. HCl/MeOH (50/50), overnight, room T°; (c) 6.0 equi. $NaHCO_3$, 1.3 equi. $CSCl_2$, $MeOH/H_2O$, room T°

**Scheme 10** Synthetic route planned for the preparation of **101-103**

The route planned for the synthesis of guanidinylating agents of type **C** is presented in scheme 11 and started with the mono-BOC protection of diaminoalkanes. This was achieved by reacting the diamines with 0.1 equivalent of di-*tert*-butyl dicarbonate as reported by Muller and co-workers (80-90% yields, based on di-*tert*-butyl dicarbonate).[132] The free amino group of **83-85** was then converted into an isothiocyanate functional group (compounds **86-88**) using two equivalents of thiophosgene in presence of one equivalent of calcium carbonate. Nucleophilic attack of ammonia (aqueous solution) onto **86-88** yielded thioureas **89-91** that were subsequently BOC-protected using two equivalents of both sodium hydride and di-*tert*-butyl dicarbonate. This afforded a mixture of N-mono and N,N'-di-BOC-

protected thioureas **92-94** but no separation was undertaken as it was believed that all products would successfully undergo guanidinylation with **53**. The coupling step was achieved using analogous $HgCl_2$-promoted guanidinylation described in section 2.1, which gave a mixture containing di-BOC-protected morphinans **95-97** and their mono-BOC-protected analogues. These were subsequently stirred overnight at room temperature in a mixture of methanol/conc. HCl (50/50), affording deprotected derivatives **98-100**.




**83** n = 2
**84** n = 4
**85** n = 6

**86** n = 2
**87** n = 4
**88** n = 6

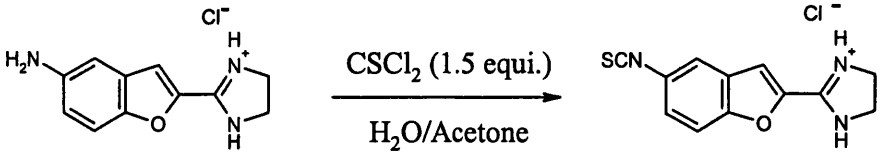
**89** n = 2
**90** n = 4
**91** n = 6

**92** n = 2
**93** n = 4
**94** n = 6

(a) 0.1 equi. $(Boc)_2O$, $CHCl_3$, 24 hrs, room T°; (b) 1.0 equi. $CaCO_3$, 2.0 equi. $CSCl_2$ $CHCl_3/H_2O$, 24 hrs, room T°; (c) 10 equi. conc. $NH_4OH$, Acetone, 24 hrs, room T°; (d) 2.0 equi. NaH, 2.0 equi. $(Boc)_2O$, dry THF, overnight, room T°

**Scheme 11** Synthetic route used for the preparation of guanidinylating agents **92-94**

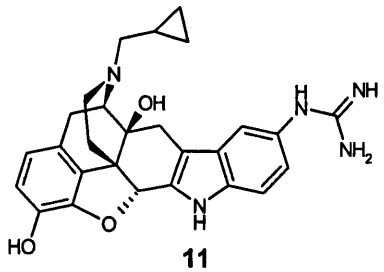
The last step of the synthesis involved conversion of **98-100** into the corresponding isothiocyanates. Previously, it has been shown within our group that the preparation of an isothiocyanate from an aniline can be achieved in presence of the hydrochloride salt of an imidazoline ring by using acetone/water as the solvent mixture (see scheme 12).[133]



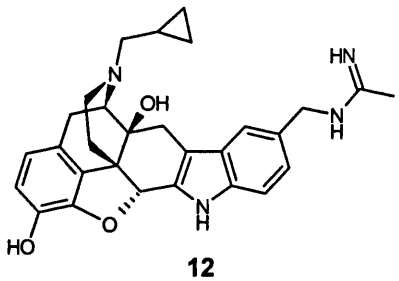

**Scheme 12** Previous preparation of an isothiocyanate from the corresponding aniline

Thus, we attempted an equivalent procedure for the preparation of target compounds **101-103** from the hydrochloride salts of **98-100**; the free base of the terminal ammonium group was first generated *in-situ* in a mixture of acetone/water by using an excess of sodium hydrogencarbonate and was subsequently reacted with 1.3 equivalents of thiophosgene. However, this procedure failed to give the desired products, probably as a direct consequence of the reacting conditions; a high proportion of water in the acetone/water solvent system was indeed required to dissolve amines **98-100** because of their highly protonated state. It is possible that the tiny amount of thiophosgene used in the reaction (a few μL) was partially destroyed in presence of water before reacting with the amines; this resulted in a complex mixture of materials that could not be purified by column chromatography due to the highly polar nature of the compounds.

Although the synthetic pathway did not lead to the target compounds, it would be interesting to evaluate the pharmacological profile of these amines as they might represent useful peripheral κ-selective antagonists. GNTI **(11)** has indeed been suggested to penetrate into the brain to a lesser extent than ANTI **(12)** because of the higher pKa of the guanidinium group compared to that of the amidinium group.[39] Thus, systemic administration of GNTI, at doses up to 10 mg/kg, was ineffective in providing anti-depressant effects (forced swim test) whereas administration of an equivalent dose of ANTI proved successful. We believe that the extra ammonium group present in compounds **98-100** will further impair access through the BBB, thus possibly restricting the bioavailability of the drugs to peripheral sites. Amines **98-100** have therefore been sent for pharmacological evaluation.



**11**

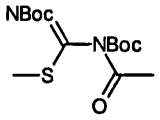


**12**

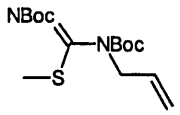
*2.3.2.b Synthesis with guanidinylating agents bearing a terminal phthalimido-protected amino group*

Since the preparation of guanidinylating agents modelled on **58** proved more tedious than that modelled on **54**, we decided to return to using the latter. It was thus

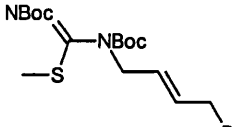
planned to react the conjugate base of **54** with electrophiles that could be later transformed into amino derivatives. However, attempts employing acrylonitrile or acrolein as such electrophiles proved unsuccessful despite varying the reacting conditions, including time, temperature or amount of base and electrophile (entries 1-5 table 2). The reactivity of **54** was then evaluated with bromobutane and bromo- and chloroacetyl chloride but all attempts proved again unsuccessful (entries 6 to 10). It was finally possible to successfully react **54** by using 3 equivalents of sodium hydride, 2 equivalents of allyl bromide or acetyl chloride and heating the reaction mixture, which afforded compounds **104** and **105** (entries 12 and 15). This led us to react **54** with 1,4-dibromo-2-butene and 4-chlorobutyryl chloride, leading respectively to analogues **106** and **107** that could be further converted into amino derivatives.



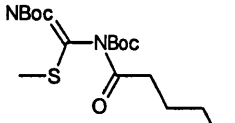

**104**




**105**

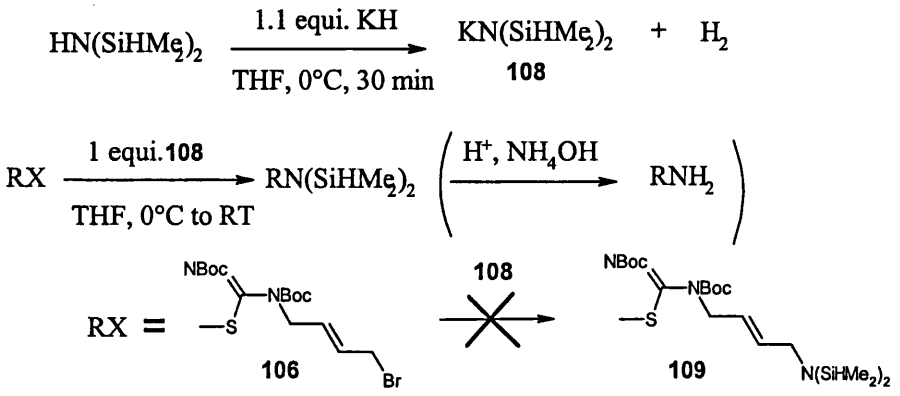



**106**




**107**

Unfortunately, attempts to react the more reactive compound, allyl bromide **106**, with potassium cyanide proved unsuccessful despite following a general procedure reported in the literature.[134] Since Itsuno *et al.* have reported that alkyl halides can be directly converted into protected amines by using potassium 1,1,3,3-tetramethyldisilazide **(108)**,[135] it was hoped that similar treatment of **106** with **108** would lead to **109** (see scheme 13). In our case, **108** was replaced by the sodium salt, prepared from commercially available 1,1,3,3-tetramethyldisilazane with sodium hydride, but subsequent reaction with **106** led unfortunately to the recovery of **106**.




**Scheme 13** Synthetic route planned for the preparation of **109**

| Reagents [i] | Conditions used | Result |
|---|---|---|
| Acrylonitrile (1 equi.)<br>Sodium hydride (1 equi.) | reaction at room temperature for 24 hours | unreacted starting materials |
| Acrylonitrile (1.1 equi.)<br>Sodium hydride (1.2 equi.) | reaction at room temperature for 5 days | unreacted starting materials |
| Acrylonitrile (1 equi.)<br>Sodium hydride (1 equi.) | reaction at 72°C for 40 hours | no trace of product |
| Acrylonitrile (2 equi.)<br>Sodium hydride (3 equi.) | reaction at 70°C for 25 hours | no trace of product |
| Acrolein (1.1 equi.)<br>Sodium hydride (1.2 equi.) | reaction at 48°C for 24 hours | no trace of product |
| Bromobutane (1.1 equi.)<br>Sodium hydride (1.2 equi.) | reaction at 48°C for 24 hours | no trace of product |
| Bromobutane (1.1 equi.)<br>Sodium hydride (1.2 equi.) | presence of 18-crown-6 (0.1 equi.)<br>reaction at 48°C for 24 hours | no trace of product |
| Chloroacetyl chloride (1.1 equi.)<br>Sodium hydride (1.2 equi.) | reaction at room temperature for 5 days | no trace of product |
| Chloroacetyl chloride (2 equi.)<br>Sodium hydride (3 equi.) | presence of 18-crown-6 (0.1 equi.)<br>attempts with heating at 58°C and 86°C | no trace of product |
| Bromoacetyl chloride (2 equi.)<br>Sodium hydride (3 equi.) | presence of 18-crown-6 (0.1 equi.)<br>attempts with heating at 58°C and 86°C | no trace of product |
| Allyl bromide (1.1 equi.)<br>Sodium hydride (1.2 equi.) | reaction at 80°C for 41 hours | no trace of product |
| Allyl bromide (2 equi.)<br>Sodium hydride (3 equi.) | reaction at 70°C for 41 hours | yield = 61 % |
| Acetyl chloride (1 equi.)<br>Sodium hydride (1 equi.) | reaction at room temperature for 25 hours | no trace of product |
| Acetyl chloride (1 equi.)<br>Triethylamine (1.1 equi.) | reaction at 50°C for 41 hours | no trace of product |
| Acetyl chloride (2 equi.)<br>Sodium hydride (3 equi.) | presence of 18-crown-6 (0.1 equi.)<br>reaction at 48°C for 24 hours | yield = 19 % |

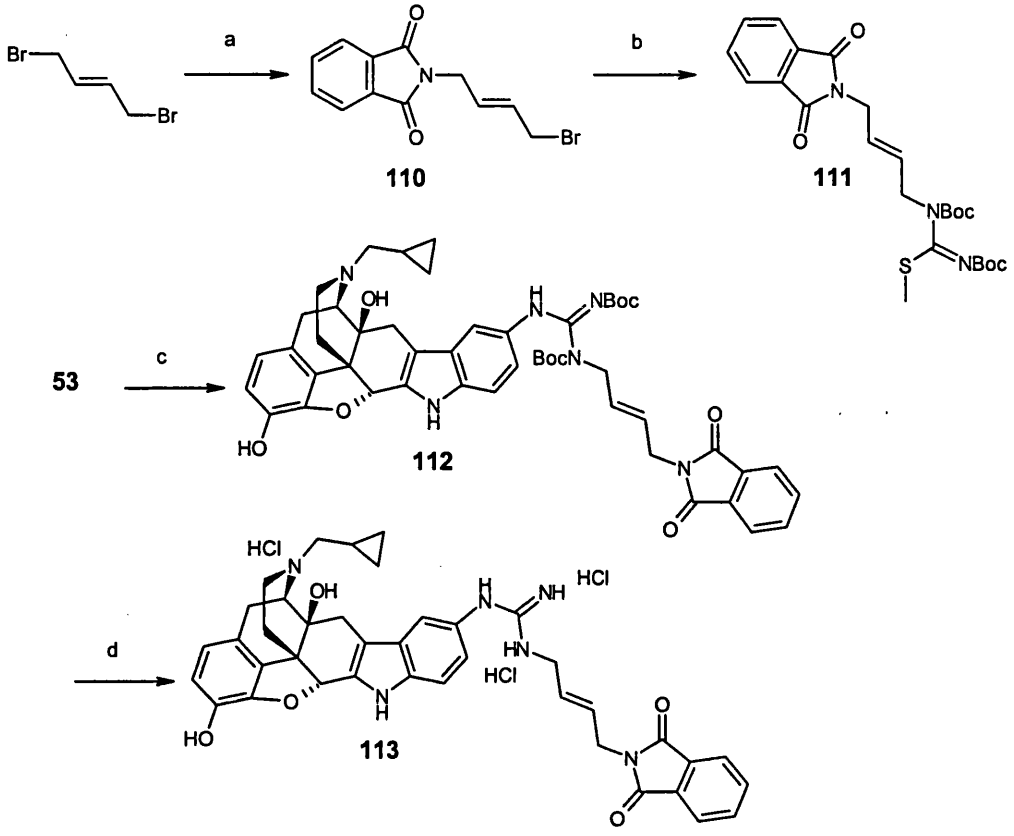
[i] : for one equivalent of 1,3-bis-BOC-2-methyl-2-thiopseudourea

**Table 2** Preliminar experiments for the preparation of guanidinylating agents

A Gabriel synthesis, one of the most popular methods used for the preparation of primary amines, was then envisaged to convert the bromo group of **106**; however, the small amount of **106** left at this stage required preparing more starting material.

Instead, we decided to react first 1,4-dibromo-2-butene with potassium phthalimide before subsequent reaction with **54**; indeed, it seemed more economically sound to proceed in this order since the first attack on 1,4-dibromo-2-butene with one equivalent of nucleophile leads to some disubstituted derivative and potassium phthalimide is much cheaper than **54**. Nucleophilic attack of potassium phthalimide on 1,4-dibromo-2-butene was achieved following a similar method reported by Langenbeck *et al.* but employing one equivalent of potassium phthalimide instead of two (scheme 14).[136] The product **(110)** was isolated in 51% yield and further reacted with **54** according to the same procedure as reported in sections 2.1 and 2.2. **111** was obtained in very good yield (80%) and subsequently coupled with **53** *via* $HgCl_2$-promoted guanidinylation, which afforded a mixture containing the desired product **112** and its mono-BOC-protected analogue. It was then proposed to remove the BOC and phthalimido protecting groups in one single step employing acidic conditions (conc. HCl/MeOH (50/50), room temperature, three days), but this afforded **113** still bearing the phthalimido protecting group; the reaction was repeated stirring the mixture at 80°C for 2 days, but this resulted in no further deprotection of **113**. Although deprotection of phthalimido groups is reported using hydrolytic (in acidic or alkaline solutions), aminolytic and hydrazinolytic (Ing-Manske) procedures, [137,138] the latter is generally the preferred method because of quicker kinetics. This led us to attempt deprotecting phthalimide **113** under hydrazinolytic conditions, first stirring **113** overnight at room temperature with 12 equivalents of hydrazine hydrate, which did not lead to full deprotection of **113**, then at 60°C with 28 equivalents of hydrazine hydrate, but this resulted in a complex mixture of materials. It seems that the primary amine was formed but could not be isolated from 2,3-dihydrophthalazine formed during the reaction. The crude product could not be purified by column chromatography because of the extreme polarity of the guanidinium salt and the side product could not be washed out with any solvent. At this stage, there was insufficient quantity of morphinan **113** to allow further work. Since strong lipophilic interactions are possible between the phthalimido group of **113** and the lipophilic pocket of the κ-receptor, in a similar manner as observed with the benzyl group of *p*-

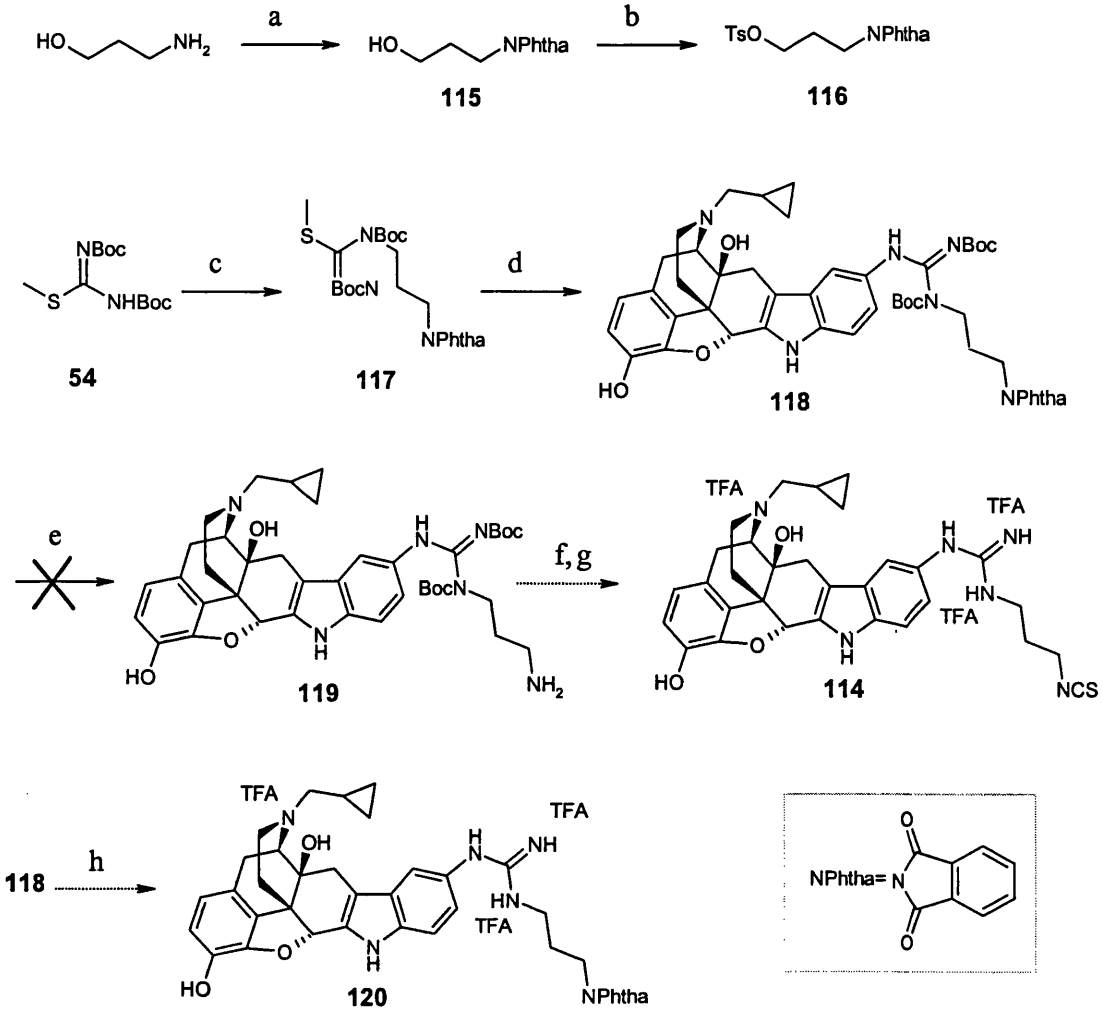
chlorobenzylGNTI (**46**), it was instead decided to send **113** for *in-vitro* pharmacological evaluation.




(a) 1.0 equi. potassium phthalimide, dry DMF, overnight, room T°; (b) 1.1 equi. NaH, 0.9 equi. **54**, dry DMF, overnight, 70°C; (c) 1.5 equi. $HgCl_2$, 2.0 equi. **111**, 2.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C; (d) conc. HCl/ MeOH (50/50), 3 days, room T°

**Scheme 14** Synthetic route used for the preparation of **113**

The problems encountered with the previous synthetic strategy led us to plan a different chronology for the removal of the protecting groups present on the guanidine moiety and on the terminal amino group, in order to allow purification of the opioid after cleavage of the phthalimido group. Moreover, we decided to use guanidinylating agents bearing a fully saturated side chain in order to afford greater flexibility of the ligand, thereby enhancing the possibility of forming a covalent bond with the receptor. Since reaction of the conjugate base of **54** with alkyl bromide proved unsuccessful (see table 2), we decided to use the synthetic pathway presented in scheme 15 (target compound **114**).




(a) 1.0 equi. N-carbethoxy-phthalimide, 1.0 equi. $NEt_3$, THF, overnight, room T°; (b) 1.0 equi. $NEt_3$, 1.0 equi. *p*-toluenesulfonyl chloride, DCM, 3 hrs, room T°; (c) 0.9 equi. NaH, 1.0 equi. **116**, dry DMF, overnight, 80°C; (d) 0.5 equi. $HgCl_2$, 0.5 equi. **53**, 1.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C; (e) 1.2 equi. $NH_2NH_2.xH_2O$, EtOH, room T°; (f) 6.0 equi. $NaHCO_3$, 1.3 equi $CSCl_2$, $CHCl_3/H_2O$, room T°, (g) = (h) DCM/TFA, overnight, room T°

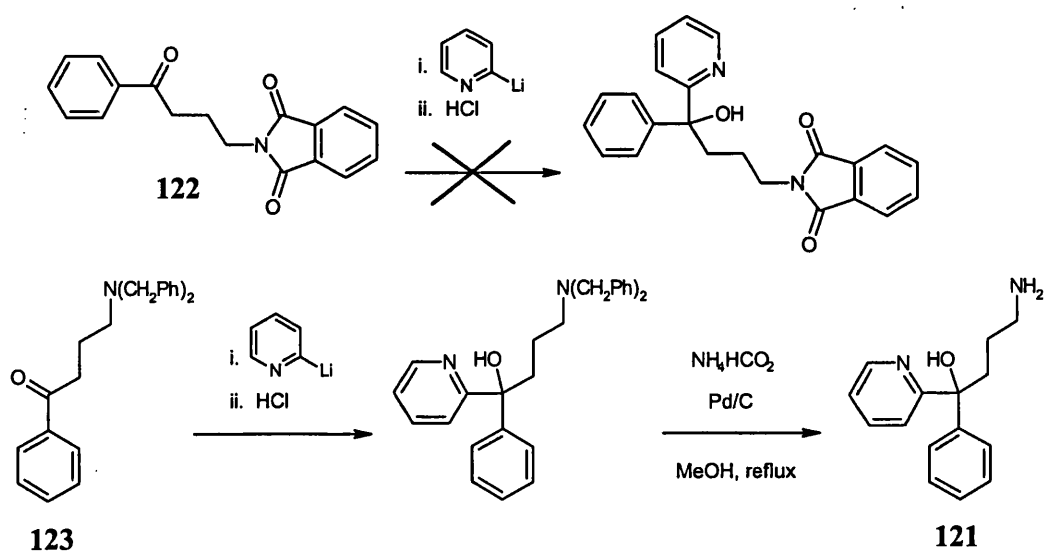
**Scheme 15** Synthetic route planned for the preparation of **114**

Phthalimido-protection of 3-aminopropanol was achieved in 86% yield, following a procedure reported by Li and co-workers, namely by reacting the amine with one equivalent of both N-carbethoxy-phthalimide and triethylamine.[139] The product 3-phthalimidopropanol **(115)** was then tosylated using *p*-toluenesulfonyl chloride in presence of either triethylamine or pyridine, both methods giving the

desired tosylate **116** with similar yields (around 60%). **116** was then reacted with the conjugate base of **54**, affording the guanidinylating agent **117** that was subsequently coupled with amine **53** according to the procedure previously described in sections 2.1 and 2.2. Unfortunately, phthalimido-deprotection of di-BOC protected morphinan **118** and its mono-BOC-analogue with 1.2 equivalents of hydrazine hydrate did not lead to the expected product **119** but to the recovery of amine **53** as a result of the high nucleophilicity of hydrazine together with the electron-withdrawing effect of the BOC groups. Basic hydrolysis of **118** with NaOH (2M aqueous solution) was then attempted but this resulted in decomposition of the starting material with no useful product being isolated. **118** was instead BOC-deprotected with trifluoroacetic acid and the corresponding salt **120** was sent for *in-vitro* pharmacological evaluation; comparison of **113** and **120** will provide information on the importance, or not, of the flexibility of the side chain in lipophilic interactions with the opioid receptors.

### *2.3.2.c Synthesis with guanidinylating agents bearing a terminal dibenzyl - protected amino group*

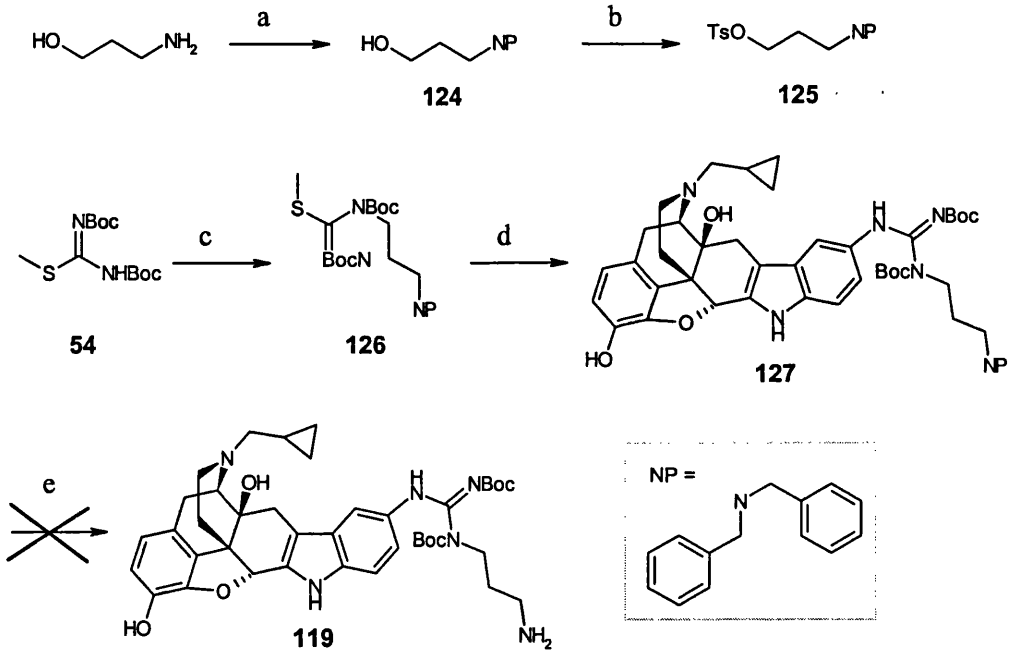
In 1991, Purchase and co-workers reported the synthesis of a pirmenol metabolite **(121)** and the synthetic route utilised is presented in scheme 16.[140]




**Scheme 16** Preparation of a pirmenol metabolite **(121)** reported in the literature [140]

Having been unsuccessful in preparing **121** *via* reaction of phthalimide **122** with 2-pyridyllithium, they decided to replace the phthalimido-protecting group by a dibenzyl-protecting group (compound **123**), which ultimately led to the successful synthesis of the target product **121**.

Although only two primary amines had been successfully prepared *via* N,N-didebenzylation at that time,[140] suggesting that the reaction was troublesome, they reported that the didebenzylation proceeded with great facility when catalytic transfer hydrogenation was used (Pd/C 10 wt. %, ammonium formate). We thus investigated whether the use of a dibenzyl-protecting group would resolve the difficulties encountered during the preparation of the irreversible ligand **114**. This led us to adopt a similar route as presented in scheme 15, but replacing the phthalimido-group with a N,N-dibenzyl protecting group (see scheme 17).

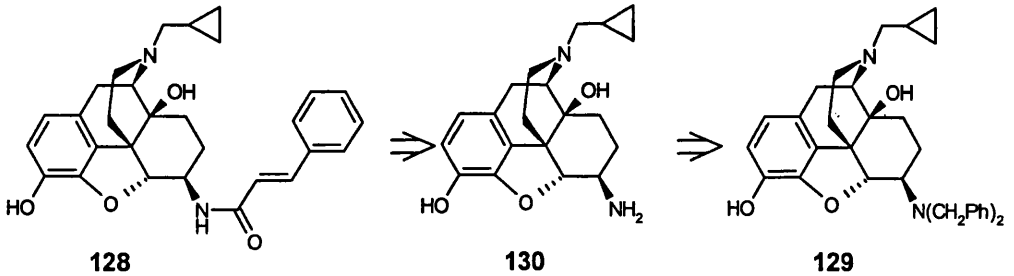



(a) 1.0 equi. benzyl bromide, DCM, overnight, room T°; (b) 1.0 equi. $NEt_3$, 1.0 equi. *p*-toluenesulfonyl chloride, DCM, 3 hrs, room T°; (c) 1.0 equi. NaH, 0.1 equi. 15-crown-5, 1.1 equi. **125**, dry DMF, overnight, 80°C; (d) 0.7 equi. $HgCl_2$, 0.5 equi. **53**, 1.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C; (e) Pd/C (10 wt. %), 20 equi. $NH_4HCO_2$, EtOH, 6 hrs, reflux or Pd/C (10 wt. %), cyclohexene/EtOH, reflux, overnight

**Scheme 17** Synthetic route planned for the preparation of **119** (route involving a dibenzyl protecting group)

The N,N-dibenzyl protecting group was introduced by stirring overnight 3-aminopropanol with one equivalent of benzyl bromide in DCM. N,N-dibenzylaminopropanol **(124)** was obtained in 42% yield and subsequently converted into its tosylate derivative **125**, using one equivalent of both *p*-toluenesulfonyl chloride and triethylamine in a similar manner as used for the preparation of **116**. Nucleophilic attack of the conjugate base of 1,3-bis-BOC-2-methyl-2-thiopseudourea **(54)** on **125** afforded the guanidinylating agent **126**, which was in turn coupled with amine **53**, yielding a mixture of mono- and di-BOC-protected morphinans **127**. Unfortunately, attempted debenzylation of the latter by transfer hydrogenation, using Pd/C and ammonium formate, resulted mainly in recovery of the starting material; monitoring of the reaction by thin-layer chromatography (TLC) showed the appearance of a weak spot that was believed to correspond to the mono-benzylated derivative but there was no evidence of formation of the desired primary amine **119**.

When preparing 6N-cinnamoyl-β-naltrexamine **(128)**, Derrick *et al.* reported that while catalytic hydrogenation of the 6N,6N-dibenzyl intermediate **129** led to the didebenzylated intermediate **130** in poor yield, transfer hydrogenation using a suspension of Pd/C in ethanol/cyclohexene afforded the desired product **130** with remarkable ease (83% yield).[141]

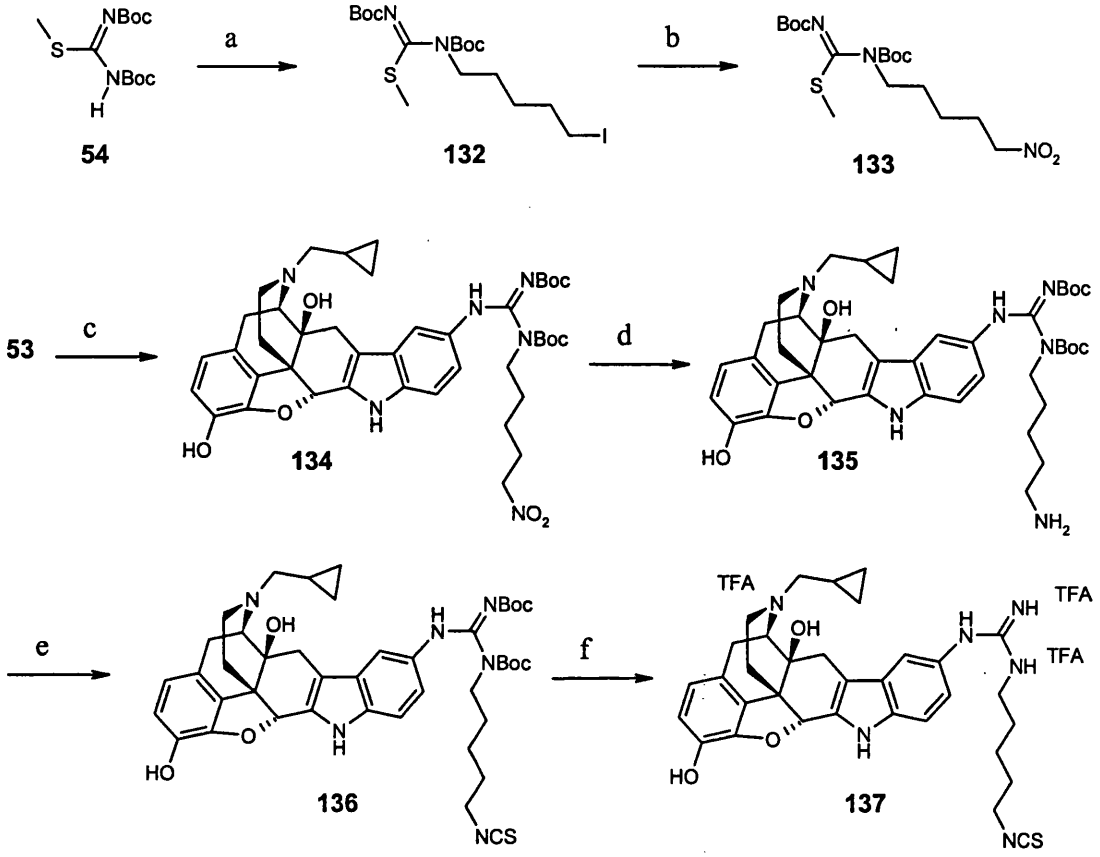



**128** **130** **129**

Thus we attempted a similar procedure for the deprotection of **127**, but this led to the same concluding remarks as when using Pd/C and ammonium formate. Since the cleavage of the dibenzyl protecting group proved uncannily troublesome, it was instead decided to remove the BOC protecting groups of **127** with an excess of trifluoroacetic acid. The corresponding product **131** was sent for binding studies in order to investigate whether the presence of benzylic groups would lead to pseudo-irreversible binding with the receptor through strong lipophilic interactions.

*2.3.2.d Synthesis with guanidinylating agents bearing a nitro precursor to the terminal amino group*

A last alternative was explored for the preparation of the targeted isothiocyanates and involved the preparation of guanidinylating agents bearing a side chain terminating with an aliphatic nitro group. It was planned to reduce the nitro group after guanidinylation with **53**; the amine would then be converted into the corresponding isothiocyanate and the BOC groups finally removed (see scheme 18).




(a) 1.0 equi. NaH, 0.1 equi. 15-crown-5, 3.3 equi. 1,5-diiodopentane, dry DMF, overnight, room T°; (b) 1.7 equi. $NaNO_2$, $DMF/H_2O$ (5/1), 2 hrs, room T°, (c) 1.4 equi. $HgCl_2$, 2.0 equi. **133**, 2.0 equi. $NEt_3$, dry DMF, 24 hrs, 60°C; (d) 9.0 equi. $FeSO_4.7H_2O$, $MeOH/H_2O/NH_4OH$, 3 hrs, 80°C; (e) 6.0 equi. $NaHCO_3$, 1.1 equi $CSCl_2$, $CHCl_3/H_2O$, 2hrs, room T°, (f) DCM/TFA, overnight, room T°

**Scheme 18** Synthetic route used for the preparation of **137**

**54** was deprotonated with one equivalent of sodium hydride and subsequently reacted with three equivalents of 1,5-diiodopentane, yielding the desired product **132**.

The conversion of halides into nitro derivatives has been reported in the literature through the use of diverse reagents including sodium nitrite,[142] silver nitrite [143] or $NaOMe/CH_3NO_2$,[144] this latter method of course extending the chain by one methylene. Given there was no particular length of side chain, we opted for the former method since the latter was reported to be low yielding; moreover, we believed that decomposition of the starting material *via* elimination was likely to occur when using $NaOMe/CH_3NO_2$. Nucleophilic displacement of iodide by sodium nitrite gave the guanidinylating agent **133**; although modest (40%), the yield obtained when stirring both starting materials in $DMF/H_2O$ (5/1) was substantially better than when stirring both starting materials in pure DMF, probably as a result of higher solubility of sodium nitrite.

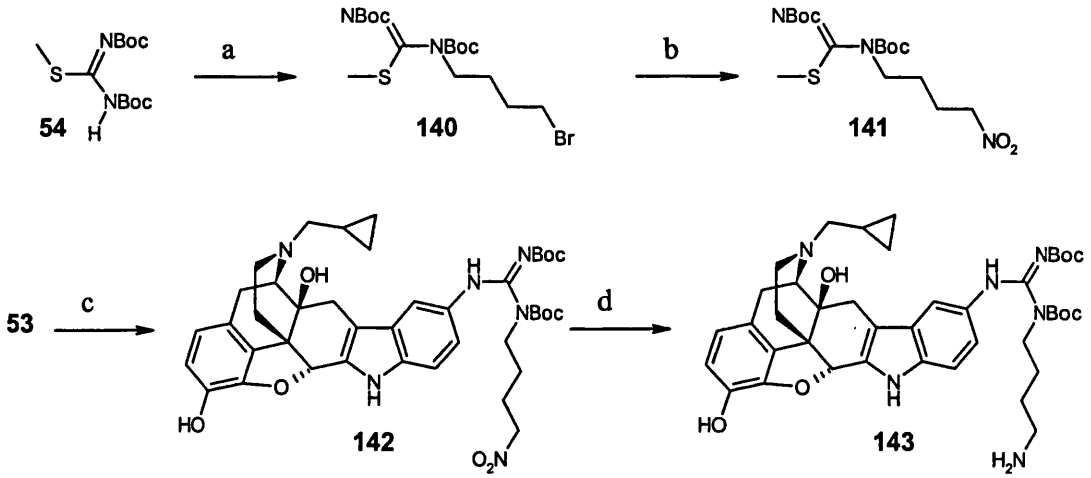
**133** was subsequently coupled with amine **53** in presence of triethylamine and mercury(II) chloride in a similar way as used in sections 2.1 and 2.2, which gave a mixture of mono- and di-BOC-protected morphinans **134**.

The reduction of aliphatic nitro compounds into primary amines has been far less investigated than the reduction of aromatic derivatives and traditionally involved the use of high pressure catalytic hydrogenation.[145] However, Ram *et al.* reported in 1984 that aliphatic nitro derivatives could be easily reduced into the corresponding amines by catalytic transfer hydrogenation (with ammonium formate as the hydrogen transfer agent) when other methods such as cyclohexene/Pd-C, hydrazine/Raney Ni, Zn/AcOH or $FeSO_4/NH_4OH$ had proved unsuccessful.[145] Other reducing agents have since been successfully used for the reduction of aliphatic nitro groups, including $LiAlH_4$, $NaBH_4/BH_3$ or more recently $NaBH_4/ZrCl_4$.[146] However, we decided to reduce **134** using either 9 equivalents of iron(II) sulfate heptahydrate or transfer hydrogenation (palladium 10 wt. % on activated carbon, ammonium formate) since these procedures appeared more convenient to us (easier procedure, quicker reaction time, less tedious workup). In both cases, the product **135** was isolated in modest yield (43% and 29% respectively).

Conversion into the corresponding isothiocyanate **136** was accomplished following the procedure reported by Korlipara and associates,[129] who used an excess of sodium hydrogencarbonate and freshly distilled thiophosgene in a biphasic $CHCl_3/H_2O$ solvent system. However, in the current work, only 1.1 equivalents of

thiophosgene were added instead of the two equivalents reported, so as to avoid possible reaction with the oxygen atoms of **135**. After two hours, monitoring of the reaction by TLC showed complete conversion of the starting material and purification by column chromatography afforded the desired product **136** in 71% yield. Finally, BOC deprotection using TFA afforded the target compound **137**.

The same synthetic strategy was utilised to target analogues of **137** bearing shorter side chains. However, nucleophilic attack of the conjugate base of **54** on 1,2-diiodoethane or 1,2-dibromoethane proved unsuccessful while reaction with 1,3-diiodopropane afforded 1,3-bis-*tert*-butoxycarbonyl-1-allyl-2-methyl-2-thiopseudo-urea **(138)**. 1,3-Diiodopropane was then replaced with 1,3-dibromopropane, which led to 1,3-bis-*tert*-butoxycarbonyl-1-(3'-bromopropyl)-2-methyl-2-thiopseudourea **(139)**. However, subsequent attempts to displace the bromo group by sodium nitrite in DMF or in a mixture of DMF/$H_2O$ (5/1) did not give the desired product. A similar two-step sequence using 1,4-dibromobutane gave somewhat better results with 1,3-bis-*tert*-butoxycarbonyl-1-(4'-bromobutyl)-2-methyl-2-thiopseudourea **(140)** isolated in 48 % yield and converted into 1,3-bis-*tert*-butoxycarbonyl-1-(4'-nitrobutyl)-2-methyl-2-thiopseudourea **(141)** in 36% yield (see scheme 19).

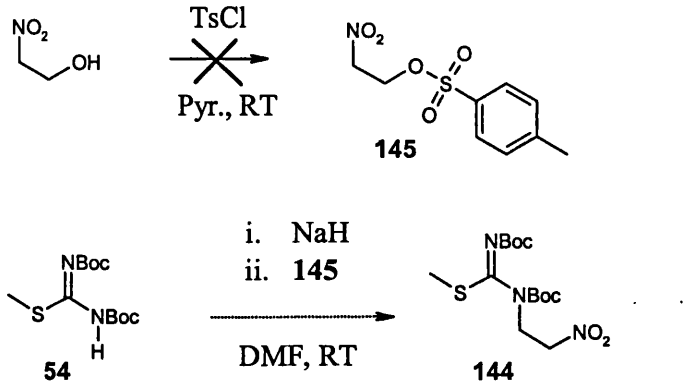



(a) 1.0 equi. NaH, 0.1 equi. 15-crown-5, 3.3 equi. 1,4-dibromobutane, dry DMF, overnight, room T°; (b) 2.0 equi. $NaNO_2$, DMF/$H_2O$ (5/1), 16 hrs, room T°; (c) 1.5 equi. $HgCl_2$, 2.0 equi. **141**, 2.0 equi. $NEt_3$, dry DMF, 48 hrs, 60°C; (d) 0.6 equi. Pd/C (10 wt. %), 20 equi. $NH_4HCO_2$, dry MeOH, 2 hrs, reflux

**Scheme 19** Synthetic route employed for the preparation of **143**

Coupling of **141** with **53** in presence of triethylamine and mercury(II) chloride afforded a mixture containing di-BOC-protected morphinan **142** and its mono-BOC-protected analogue that were subsequently reduced to **143** (mixture of mono- and di-BOC-protected morphinans) by transfer hydrogenation (palladium on activated carbon, ammonium formate). There was however insufficient material left at this stage to undertake the conversion into the corresponding isothiocyanate. However, the successful synthesis of **143** will allow the synthesis to be repeated on a larger scale.

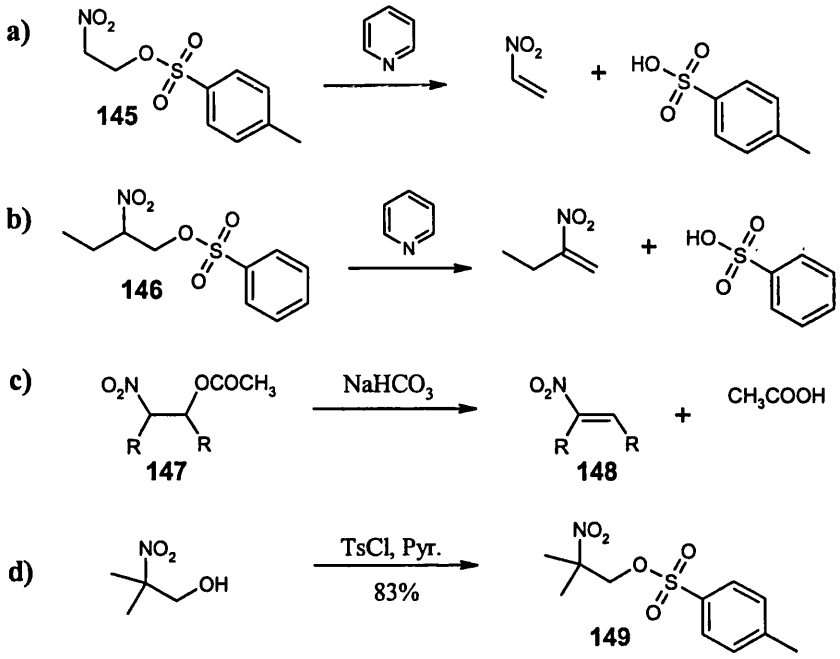
Since the synthesis of the two-carbon analogue **144** had not been possible by the route used for **133** or **141**, an alternative approach was envisaged from commercially available nitroethanol (scheme 20).




**Scheme 20** Synthetic route planned for the preparation of **144**

Unfortunately, tosylation of nitroethanol, using one equivalent of *p*-toluenesulfonyl chloride in pyridine, proved unsuccessful; it is possible that the product **145** was formed but immediately decomposed in presence of pyridine (scheme 21, reaction a). Similar decomposition was also proposed by Riebsomer who failed to isolate any ester when reacting 2-nitro-1-butanol with benzenesulfonyl chloride in pyridine.[147] He believed that the ester **146** was initially formed but immediately decomposed into benzenesulfonic acid and 2-nitro-1-butene as a consequence of the acidity of the proton attached to the carbon bearing the nitro group (scheme 21, reaction b). This was a plausible explanation since the acidity of such protons had been demonstrated in an experiment reported by Schmidt and Rutz, who found out that heating nitro esters of type **147** in presence of sodium bicarbonate led to the nitro olefin derivatives **148** (scheme 21, reaction c).[147] Of additional support is

the fact that tosylation of 2-nitro-2-methylpropanol (*ie* a nitro-alcohol lacking a proton attached to the carbon bearing the nitro group) using similar conditions as used in the present project has been reported to lead smoothly to the tosylated derivative **149** (see scheme 21, reaction d).[148]




**Scheme 21** Decomposition of arylsulfonyl esters of nitro alcohols in presence of pyridine: a consequence of acidity?

In summary, one ligand **(137)**, modelled on GNTI **(11)** and modified by the introduction of a side chain terminating with an isothiocyanate group, has been successfully prepared, while the successful synthesis of **143** should allow the preparation of the corresponding isothiocyanate.

## 2.4 Benzylnorbinaltorphimine

### *2.4.1 Rationale and design*

Since norBNI **(13)** is a highly κ-selective opioid antagonist with long lasting but surmountable effects, the present work explores the synthesis of a new irreversible ligand for the κ-opioid receptor modelled upon the structure of norBNI. It is recognised that the already long duration of action of norBNI will make assessment of relative irreversibility of analogues somewhat difficult.

*2.4.1.a Modification of norBNI: at which position?*

As already mentioned, norBNI **(13)** is a bivalent ligand, whose binding with the κ-receptor is based upon the "message-address" concept: the first pharmacophore (message component) binds to the region of the κ-receptor responsible for activity whereas the scaffold (pyrrolic spacer) of **13** rigidly holds the second basic nitrogen (address) towards the acidic residue Glu297 present within the κ-receptor. Docking studies of GNTI **(11)** (whose binding mimics that of **13**) into the κ-receptor have also suggested an ion pair interaction between N-17 and the carboxylate group of Asp138 (TM3), which was confirmed by site directed mutagenesis.[88] In addition, it was also demonstrated that the cyclopropyl methyl and phenolic moieties of the first pharmacophore of **13** are prominent in conferring affinity and activity.[88] This was later confirmed by docking studies of GNTI **(11)**, which suggested that the phenolic group might indeed interact with the imidazoline ring of His291.[102] Therefore, it was not appropriate to modify these groups and since the synthesis of unsymmetrical derivatives of norBNI has been reported to be low yielding,[102] it was decided not to modify those groups on the second pharmacophore.

With this in mind, there remain only two viable positions for the modification of **13**, namely the 14,14'-hydroxy groups and the pyrrolic nitrogen (see figure 8). It was believed that the pyrrolic group was the more readily accessible and the present project sought to investigate the possibility of conferring irreversible binding to norBNI *via* substitution of its pyrrolic nitrogen.

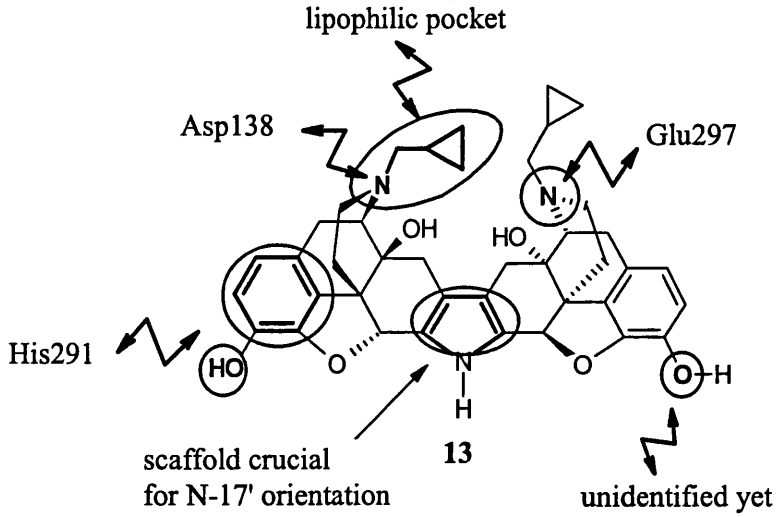
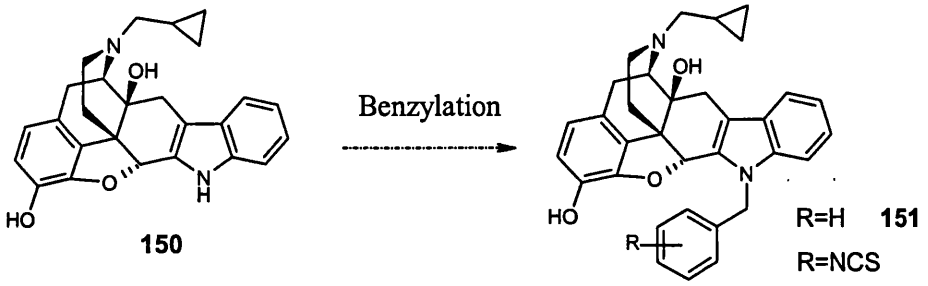



**Figure 8** The structure of norBNI **(13)**: elements crucial for κ-selectivity and activity

*2.4.1.b Modification of norBNI: which substituent?*

In 1994, Korlipara *et al.* explored the modification of the δ-selective antagonist naltrindole (NTI) **(150)** by benzyl substitution at the indolic nitrogen; this resulted in benzylnaltrindole (BNTI) **(151)** as a $\delta_2$-antagonist with longer duration of action (see scheme 22).[100] Although the effects of **151** were still surmountable, true irreversible binding *via* formation of a covalent bond with the receptor was eventually achieved by subsequent addition of an electrophilic isothiocyanate moiety onto the benzyl group.[129]



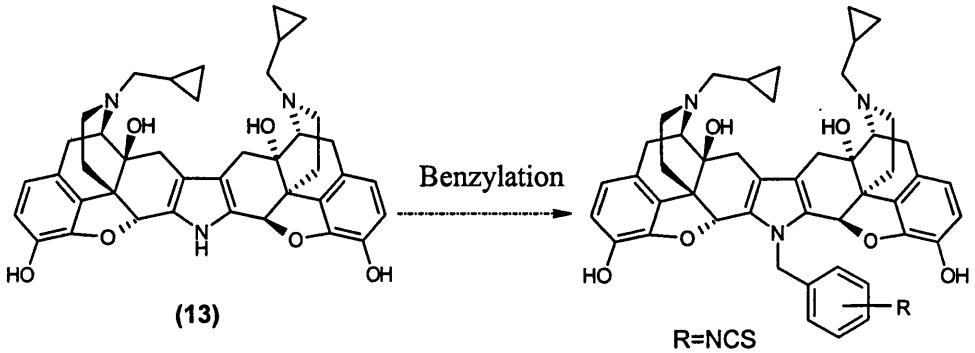

**150**

δ competitive selective antagonist

δ selective antagonist with long duration of action

**Scheme 22** Strategy employed for the design of BNTI **(151)** and analogues

Since norBNI **(13)** is already a long-lived κ-antagonist, it was of interest to investigate whether benzylation of norBNI was sufficient to produce a κ-selective irreversible or pseudo-irreversible antagonist. In addition, and in an analogous approach to that used by Korlipara,[129] subsequent incorporation of an isothiocyanate group into BnorBNI **(152)** was also planned if necessary (scheme 23).




**(13)**

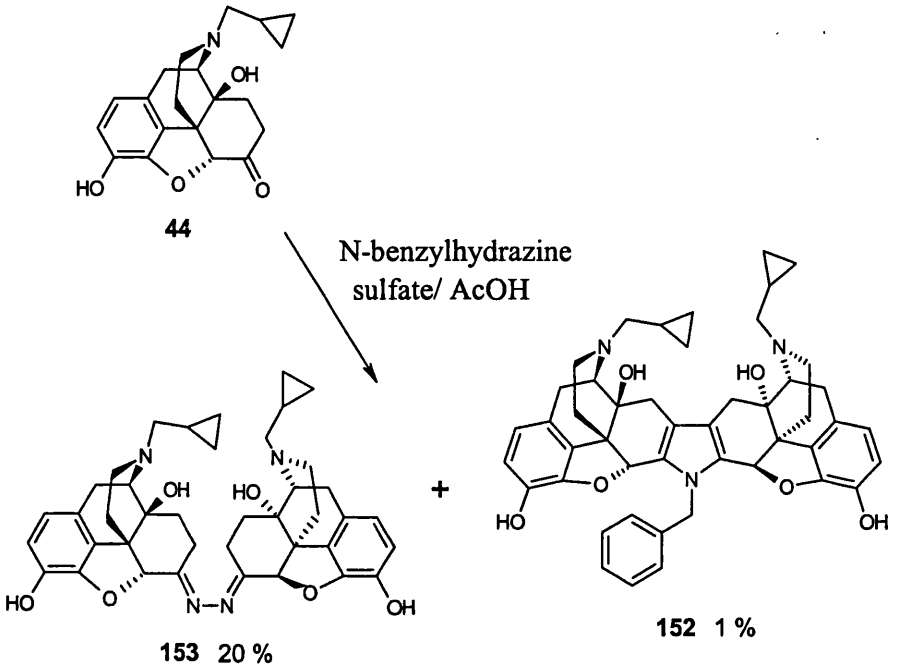
κ competitive antagonist with long duration of action

irreversible κ antagonist ?

**Scheme 23** Strategy employed for the design of BnorBNI **(152)**

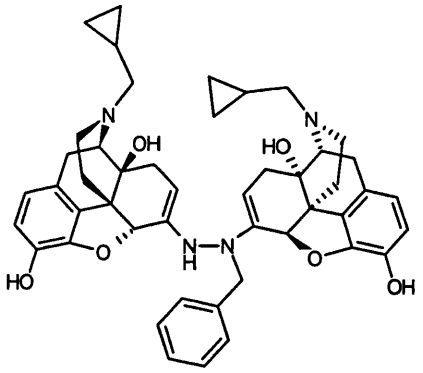
*2.4.2 Synthesis*

A synthesis of **152**, based on the method reported for the preparation of BNI **(28)** [79] and modified by the use of N-benzylhydrazine sulfate, had already been developed within our group and is presented in scheme 24.[149]



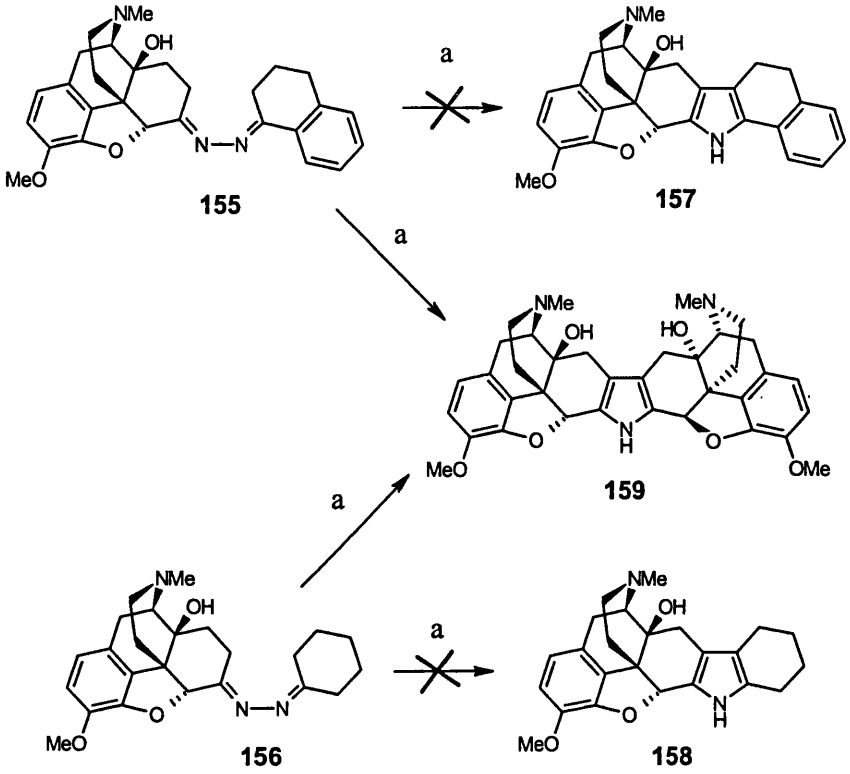

**Scheme 24** A previous synthetic approach for the preparation of BnorBNI **(152)** [149]

Although straightforward, this route was not satisfactory because of the long reaction time (9 days) and low yield reported (1%). It is noteworthy that azine **153** was isolated as a side product; although **153** could result from debenzylation of the expected intermediate **154**, it cannot be ruled out that an alternative complex rearrangement from the reaction mixture had occurred.



**154**

Schmidhammer and Schwarz have also reported unexpected reactions when stirring azines **155** and **156** with methanesulfonic acid in dry DMSO.[150] They found out that the main product isolated after reaction was inexplicably not the expected pyrroles **157** and **158** but rather bimorphinan **159** (see scheme 25).



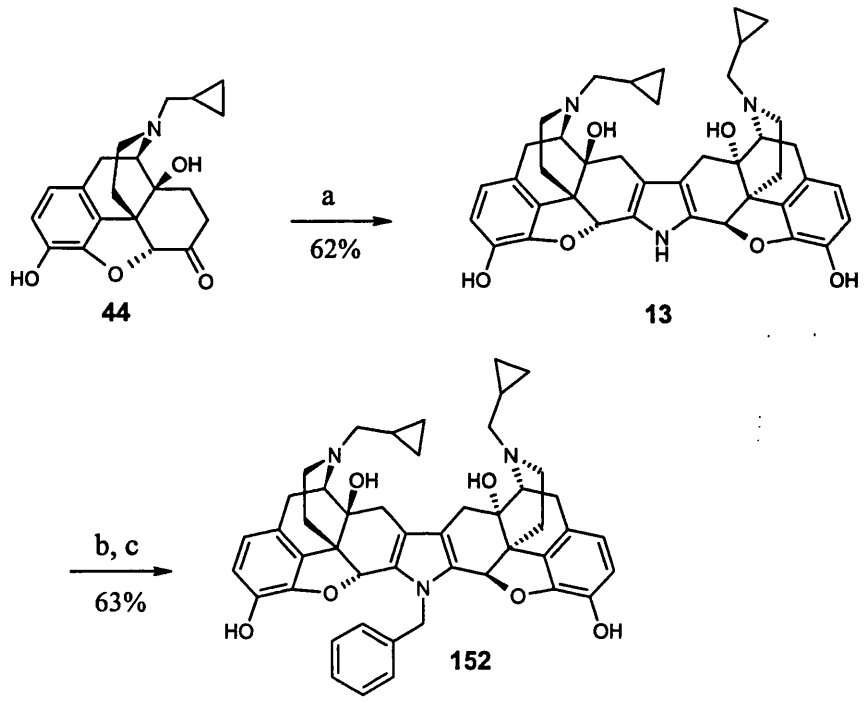

(a) $CH_3SO_3H$/DMSO, Room T°, 3 hrs

**Scheme 25** Unexpected reactions of azines in presence of methanesulfonic acid [150]

In any case, if BnorBNI had to be prepared on a larger scale, another synthetic approach was required. The method employed in the present project explored direct benzylation of norBNI **(13)**. It was believed that in presence of a large excess of strong base, benzylation of the penta-anion of **13** with one equivalent of benzyl bromide should occur at the pyrrolic nitrogen because of its higher reactivity compared to the phenoxide groups and because of less steric hindrance compared with the alkoxide groups at the 14 and 14' positions.

**13** was synthesised from naltrexone **(44)** according to the Piloty procedure used by Ivy Carroll, except that hydrazine hydrochloride was replaced with hydrazine sulfate.[151] Deprotonation of **13** with 10 equivalents of sodium hydride and subsequent benzylation with one equivalent of benzyl bromide led to the quantitative addition of one benzyl group onto the starting material as expected; however, NMR analysis showed that the reaction had not occurred at the targeted pyrrolic site but most probably at one of the hydroxyl groups.

This led us to envisage the formation of BnorBNI **(152)** in several steps, namely benzylation of **13** with three equivalents of benzyl bromide followed by debenzylation of the phenolic benzyl ethers under acidic conditions, as it was believed that, once formed, the benzylated pyrrolic group should remain stable under such conditions (see scheme 26).




**44** **13** **152**

(a) 0.53 equi. $NH_2NH_2.H_2SO_4$, dry DMF, 6 hrs, 100°C then 0.51 equi. $CH_3SO_3H$, DMSO, 3.5 hrs, 130°C; (b) 10.0 equi. NaH, 0.25 equi. 18-crown-6, 3.0 equi. BnBr, DMF, 43 hrs, room T°; (c) HCl/MeOH (50/50), 40 hrs, 90°C

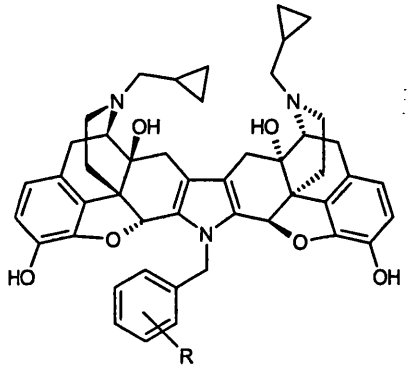
**Scheme 26** Total synthesis of BnorBNI **(152)**

Deprotonation of **13** with ten equivalents of sodium hydride and subsequent benzylation with three equivalents of benzyl bromide afforded a mixture of tri- and pentabenzyl-substituted norBNI. The fact that no starting material was left at the end of the reaction and that some penta-substituted product was obtained when using only three equivalents of benzyl bromide suggested that some decomposition had occurred during the reaction or during the purification. The mixture of tri- and pentabenzyl-substituted norBNI was immediately treated with a mixture of methanol/conc. HCl (50/50) at 90°C; this gave after purification benzylnorbinaltorphimine **(152)** in a 40% overall yield from naltrexone, a hugely improved yield compared to the first method employed within our group for the preparation of **152** (1% yield).

## 2.5 Irreversible ligands modelled on benzylnorbinaltorphimine (152)

### *2.5.1 Rationale*

We decided to investigate whether introduction of an isothiocyanate group onto the benzyl ring of BnorBNI would result in covalent binding with the receptor and whether such modification would have an influence on the selectivity and/or affinity of the parent compound. It was thus proposed to synthesize the *o*, *m*, and *p* isothiocyanate regioisomers **160, 161, 162, 163, 164,** and **165** derived from the equivalent anilines **166, 167** and **168** and benzylamines **169, 170** and **171.**

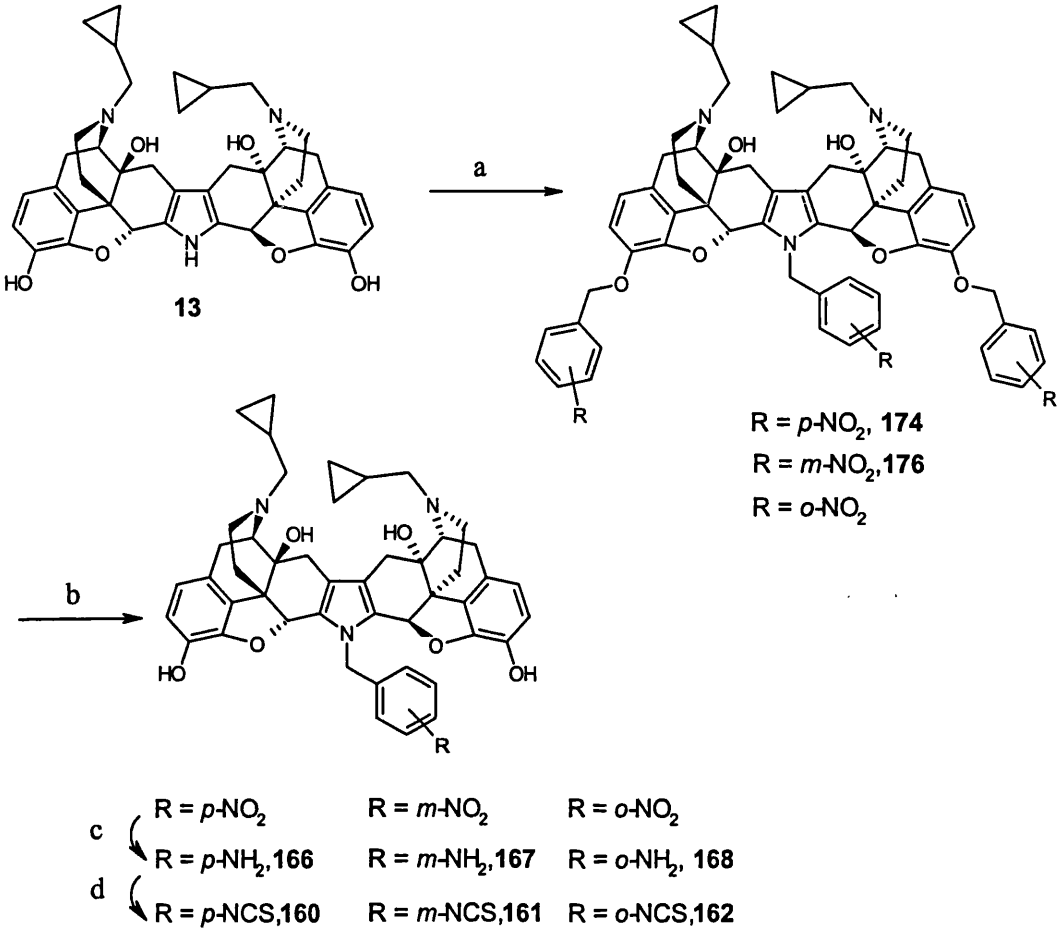



| | |
|---|---|
| R = *p* NCS **160** | R = *p* $NH_2$ **166** |
| R = *m* NCS **161** | R = *m* $NH_2$ **167** |
| R = *o* NCS **162** | R = *o* $NH_2$ **168** |
| R = *p* $CH_2NCS$ **163** | R = *p* $CH_2NH_2$ **169** |
| R = *m* $CH_2NCS$ **164** | R = *m* $CH_2NH_2$ **170** |
| R = *o* $CH_2NCS$ **165** | R = *o* $CH_2NH_2$ **171** |

### *2.5.2 Synthesis of compounds 160-162*

Since the synthetic strategy employed for the preparation of BnorBNI **(152)** gave satisfactory results, we decided to employ a similar route for the synthesis of **160-162,** but replacing benzyl bromide with suitable alternatives; the use of nitro groups as precursors to isothiocyanates proving successful for the preparation of irreversible benzylGNTI analogues (section 2.3.2.d), it was planned to benzylate

norBNI (**13**) with *o*-, *m*- and *p*-nitrobenzyl halides. The synthetic approach is presented in scheme 27.



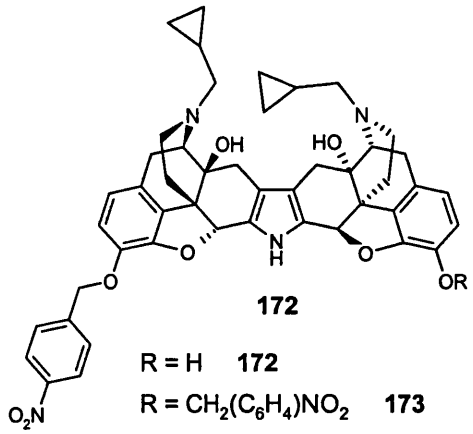

(a) 10 equi. NaH, 3 equi. $NO_2C_6H_4CH_2X$, DMF, overnight, 70°C; (b) HCl/MeOH (50/50), overnight, 80°C; (c) 9 equi. $FeSO_4.7H_2O$, $MeOH/H_2O/NH_4OH$, 3 hrs, 80°C; (d) 6 equi. $NaHCO_3$, 1.2 equi. $CSCl_2$, $CHCl_3/H_2O$, room T°

**Scheme 27** Synthetic route planned for the preparation of **160, 161** and **162**

Deprotonation of norBNI (**13**) with ten equivalents of sodium hydride, followed by nucleophilic attack on readily-available *p*-nitrobenzyl chloride (three equivalents, room temperature) led to a mixture of mono- and di-benzylated products **172** and **173** in 10% and 30% yield respectively; no expected product **174** was isolated, probably as a consequence of the low nucleophilicity of the pyrrolic nitrogen together with the low reactivity of *p*-nitrobenzyl chloride.

*p*-Nitrobenzyl bromide was then utilised due to the better leaving group properties of bromide, though it was acknowledged that the deactivating nitro group might still prevent reaction; this was indeed confirmed since benzylation of **13** using *p*-nitrobenzyl bromide, stirring the reaction mixture at 60°C, led to the same result as before with only phenolic ether products isolated. Reaction of the conjugate base of **13** with *p*-nitrobenzoyl chloride also failed to give the desired product despite several similar benzoylations of pyrrolic nitrogens reported in the literature.[152] Though direct benzylation of **13** did not give the desired product, it was felt desirable to use **173** to confirm whether the necessary 3,3'-O-debenzylations could be achieved before trying to improve the benzylation step. Thus, **173** was stirred overnight at 80°C in a mixture of methanol/conc. HCl (50/50) but this led only to unreacted starting materials.

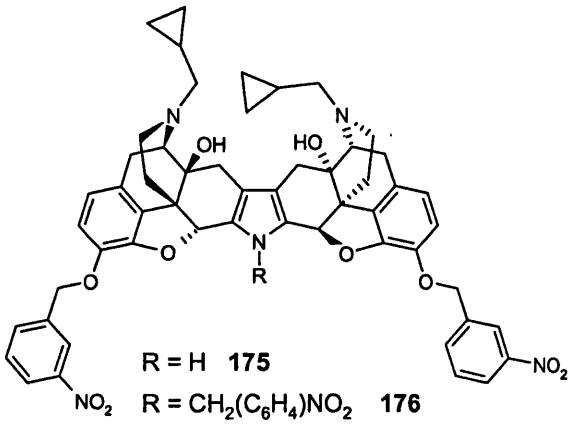
Since nitro groups are less deactivating in *m*-position, benzylation of the penta-anion of **13** with three equivalents of *m*-nitrobenzyl bromide was carried out, initially stirring at room temperature then warming to 52°C overnight. This gave two fractions, the main one being identified as the di-substituted product **175** and the other as the desired tri-substituted product **176** (28% yield). Unfortunately, stirring **176** overnight in a mixture of methanol/conc. HCl (50/50) at 94°C resulted in recovery of the tri-benzylated starting material.




**172**

R = H **172**

R = $CH_2(C_6H_4)NO_2$ **173**

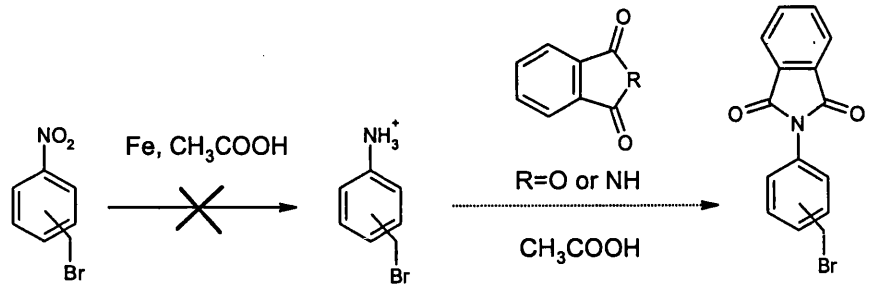



R = H **175**

R = $CH_2(C_6H_4)NO_2$ **176**

As the difficulties in both introducing the benzyl group at the pyrrolic nitrogen and its subsequent removal from the phenolic hydroxyls appeared to be due to the electron-withdrawing effect of the nitro group, it was decided to convert the nitro group of the benzyl bromides into a protected amino group before subsequent benzylation of **13**. In order to avoid polymerisation of the aminobenzyl bromides,

both reduction and protection would have to be achieved under acidic conditions, which led us to envisage the synthetic route presented in scheme 28.



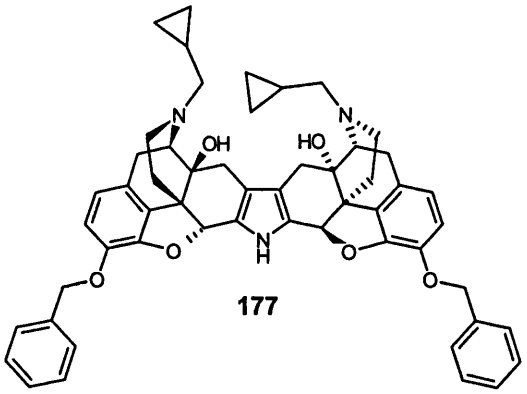

**Scheme 28** Synthetic route planned for the preparation of benzyl bromide derivatives

Broggini *et al.* have reported that quantitative reduction of nitrobenzyl derivatives into the corresponding amines can be achieved when refluxing the former for 3 hours with iron powder in ethanol/acetic acid (20% aqueous solution).[153] Reduction of *p*-nitrobenzyl bromide was thus attempted following an equivalent procedure, first stirring the reaction mixture at room temperature then under reflux, but unfortunately this proved unsuccessful.

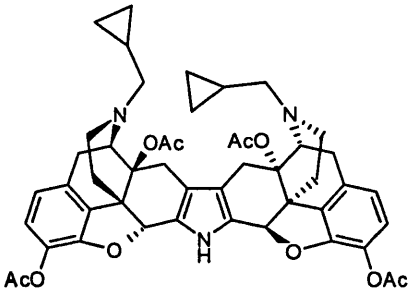
The reactivity of the pentaanion of **13** was then evaluated with α-bromo-*p*-tolunitrile. The groups added at 3- and 3'-positions would then be removed before hydrogenating the nitrile moiety. However, stirring **13** with 10 equivalents of sodium hydride before adding three equivalents of α-bromo-*p*-tolunitrile did not afford any useful product.

Although it is acknowledged that the pentaanion of norBNI could be successfully reacted with benzyl bromide, it appeared that the poor solubility of the pentaanion, in combination with other parameters such as low reactivity of the electrophiles, could be prejudicial to the success of the reaction. As we had already shown during the synthesis of **152** that **13** could be readily benzylated (section 2.4) and that the phenolic benzyl ethers were readily cleaved under acidic conditions, it was decided to first protect the phenolic hydroxyls of **13** with benzyl groups. This was achieved in quantitative yield by stirring **13** overnight in DMF with 1.5 equivalents of potassium carbonate and 2.5 equivalents of benzyl bromide. The product **(177)** was then deprotonated with 10 equivalents of sodium hydride and reacted with 5 equivalents of *p*-nitrobenzyl bromide, but this resulted in recovery of **177**.

This led us to envisage the protection of all four hydroxy groups of **13**; we opted for an acetate protecting group since this group had been successfully used by Nelson and colleagues for the protection of 3- and 14-hydroxy groups of naltrexone-derived ligands, with its deprotection being achieved with remarkable ease (this will be discussed later).[154,155] A procedure for the preparation of the tetraacetyl **178** was reported by Portoghese and involved stirring **13** in acetic anhydride and pyridine for 2 days at 24°C.[102] The esterification was initially postulated to occur *via* formation of acylonium groups in 17- and 17'-positions of **13** followed by intramolecular transfer to the neighbouring hydroxyls (14- and 14'-positions), hence explaining the remarkable ease of the tetraacylation.[102] It seems however more likely that the basic nitrogens in 17- and 17'-positions act as hydrogen acceptors from the 14- and 14'-hydroxyls, thereby resulting in higher nucleophilicity of the oxygen atoms.[156]



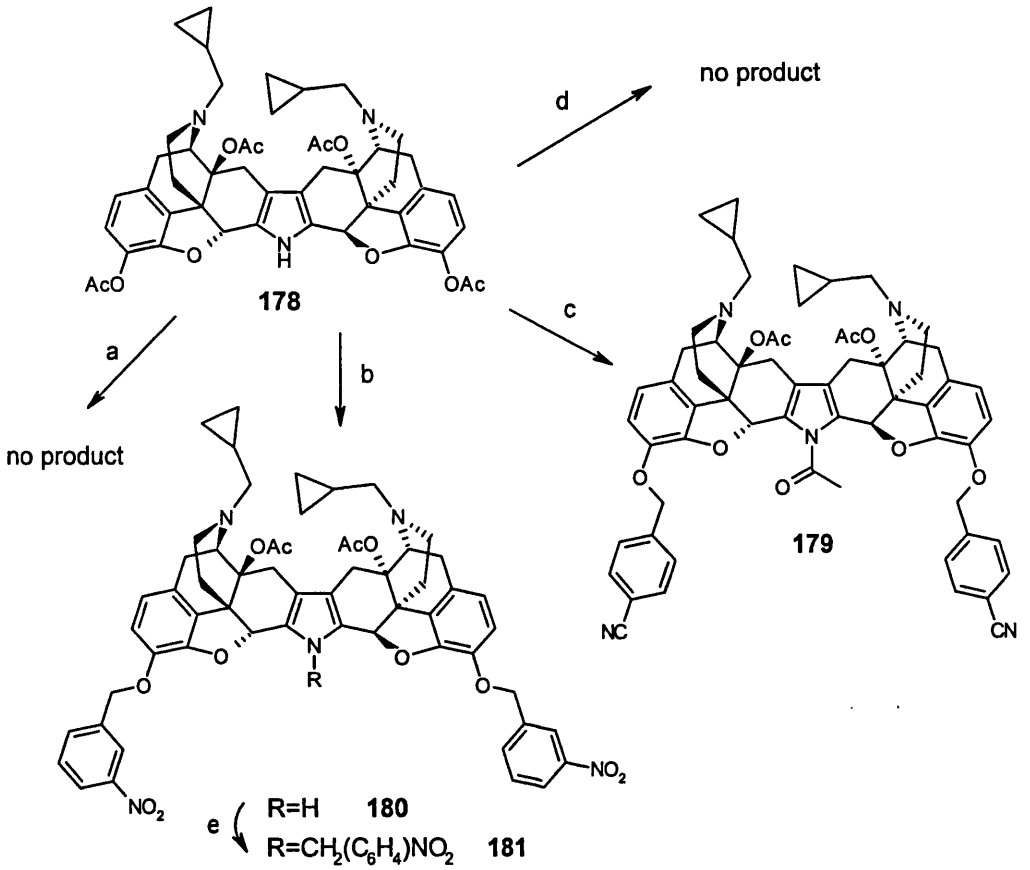

**177**




**178**

However, we instead decided to prepare **178** by refluxing **13** in acetic anhydride since we believed that the reaction would reach completion in a much shorter time; **178** was indeed obtained in quantitative yield after stirring the reaction mixture for only two hours. The tetraacetyl compound was subsequently deprotonated with sodium hydride and reacted with an excess of *p*-nitrobenzoyl chloride, *p*-nitrobenzyl bromide, *m*-nitrobenzyl bromide and α-bromo-*p*-tolunitrile. The results are presented in figure 9: no desired product was isolated in any case while reactions with α-bromo-*p*-tolunitrile and *m*-nitrobenzyl bromide afforded the di-substituted products **179** and **180** respectively. These products seem to arise from cleavage of the acetate esters in 3- and 3'-positions before nucleophilic attack of the phenoxide groups onto the benzyl bromide derivatives; it is noteworthy that the acyl group has

moved to the pyrrolic nitrogen in the former case. **180** was further reacted with *m*-nitrobenzyl bromide, which gave the desired tri-substituted product **181**. However, the overall yield (11%) prompted us to find another synthetic route.

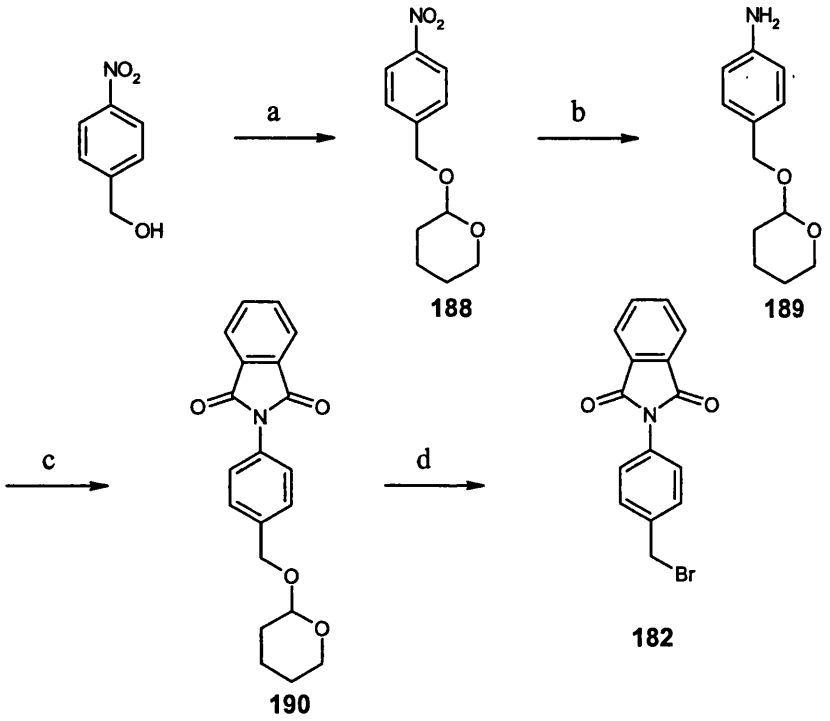



(a) 4.0 equi. NaH, then 1.2 equi. *p*-$NO_2C_6H_4COCl$, dry THF, overnight, 60°C; (b) 4.4 equi. NaH, then 2.0 equi. *m*-$NO_2C_6H_4CH_2Br$, dry THF, overnight, 60°C; (c) 10.0 equi. NaH, 0.1 equi. 18-crown-6, then 2.0 equi. *p*-$NC(C_6H_4)CH_2Br$, dry THF, 2 days, room T° then 6hrs, 70°C; (d) 10.0 equi. NaH, 0.1 equi. 18-crown-6, then 3.0 equi. *p*-$NO_2C_6H_4CH_2Br$, dry THF, overnight, 60°C; (e) 10.0 equi. NaH, then 3.0 equi. *m*-$NO_2C_6H_4CH_2Br$, dry THF, overnight, 60°C

**Figure 9** Attempted pyrrolic N-substitutions of **178**

Again, it was believed that replacing the deactivating nitro and cyano groups of the benzyl bromides with protected amino groups should result in greater facility of pyrrolic N-benzylation. We opted for a phthalimido-protecting group as it would remove both protons from the nitrogen of the aminobenzyl bromides and therefore alleviate problems likely to be encountered when using sodium hydride for the

subsequent deprotonation and benzylation of **178**. We planned to prepare *p*-, *m*- and *o*-phthalimidobenzyl bromides **182, 183** and **184** from the corresponding aminobenzyl alcohols **185, 186** and **187** by protecting first the hydroxy groups, since preliminary attempts to react **187** with phthalimide or phthalic anhydride had failed to give the desired product. The choice of *tert*-butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP) protecting groups appeared most attractive for this purpose, as THP- and TBDMS-ethers can be directly converted into the corresponding bromides. Although **185** is commercially available, it is either expensive or of unsatisfactory quality depending on the source; this prompted us to start the synthesis, in this particular case, with the nitro-analogue (see scheme 29).




(a) 1.0 equi. 3,4-dihydro-2*H*-pyran, 0.01 equi. *p*-toluenesulfonic acid monohydrate, $CHCl_3$, overnight, room T°; (b) 0.03 equi. Pd/C (10 wt. %), EtOH, $H_2$, overnight, room T°; (c) 1.0 equi. phthalic anhydride, xylenes (mixed), reflux, overnight; (d) 2.0 equi. $PPh_3$, 2.0 equi. imidazole, 2.0 equi. $Br_2$, dry DCM, 3 hrs, room T°

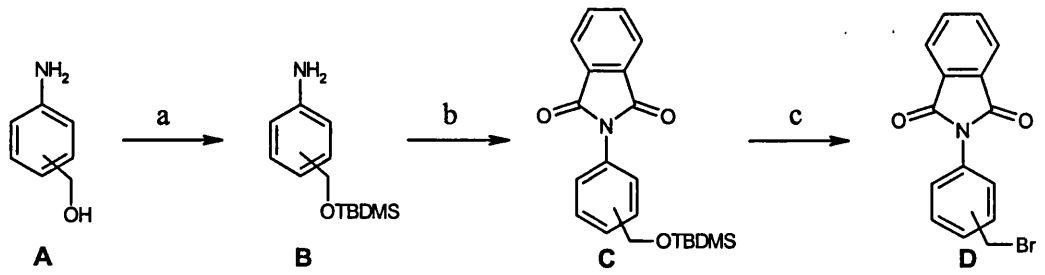
**Scheme 29** Preparation of *p*-phthalimidobenzyl bromide **(182)**

Tosic acid-catalysed addition of 4-nitrobenzyl alcohol on one equivalent of 3,4-dihydro-2*H*-pyran gave the THP-protected derivative **188** that was subsequently

reduced to the corresponding aniline **189** *via* standard catalytic hydrogenation (room temperature, Pd/C, ethanol, hydrogen). Subsequent attempts to react **189** with one equivalent of phthalimide in boiling xylenes (mixed) failed to yield the desired product; however, reaction with phthalic anhydride, using a modified procedure based on reaction of aniline with phthalic anhydride in *p*-cymene,[157] proved somewhat successful, with **190** isolated in 16% yield.

Direct conversion of THP ethers into the corresponding bromides is most commonly achieved using $PPh_3/CBr_4$. In some specific cases, such as bromination of THP ethers of secondary alcohols, the use of these reagents has however proved unsuccessful and other reagents such as triphenylphosphine and 2,4,4,6-tetrabromo-2,5-cyclohexadienone were required.[158] For **190**, the standard conditions were sufficient, with the desired product **182** readily obtained in 3 hours when using bromine, triphenylphosphine and imidazole (60% yield).

Surprisingly, *o*-phthalimidobenzyl bromide could not be prepared by an analogous route as THP-protection of 2-aminobenzyl alcohol with 3,4-dihydro-2*H*-pyran failed to give the desired product. An alternative protecting group was thus required and the TBDMS protecting group appeared to be suitable; the new synthetic route is presented in scheme 30.




| | *p* | *m* | *o* |
|---|---|---|---|
| **A =** | **185** | **186** | **187** |
| **B =** | **191** | **192** | **193** |
| **C =** | **194** | **195** | **196** |
| **D =** | **182** | **183** | **184** |

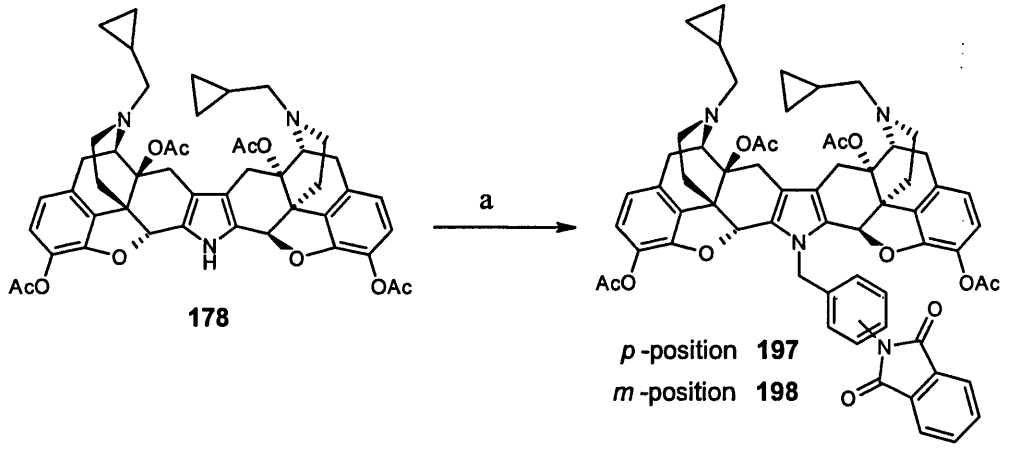
(a) 1.5 equi. *tert*-butyldimethylsilyl chloride, 2.0 equi. imidazole, dry THF, overnight room T°; (b) 1.0 equi. phthalic anhydride, mixed xylenes, overnight, reflux; (c) 1.2 equi. triphenylphosphine, 1.2 equi. $Br_2$, dry DCM, 3 hrs, room T°

**Scheme 30** Preparation of phthalimidobenzyl bromides **182, 183** and **184** (synthetic route using TBDMS protection)

Since the previous route did not provide sufficient *p*-phthalimido benzyl bromide **(182)**, we decided to repeat the preparation of this compound according to this new strategy. This involved first preparing 4-aminobenzyl alcohol; this was achieved by reducing the nitro analogue *via* standard hydrogenation procedure (Pd/C, ethanol, hydrogen, room temperature), which afforded the desired product **185** in 67% yield, along with a side-product identified as *p*-toluidine (17% yield).

The aminobenzyl alcohols **185, 186** and **187** were quantitatively protected into TBDMS ethers **191, 192** and **193** by stirring overnight at room temperature with 1.5 equivalents of *tert*-butyldimethylsilyl chloride and 2.0 equivalents of imidazole. The anilines were subsequently refluxed in mixed xylenes with one equivalent of phthalic anhydride, which afforded **194, 195** and **196** in 96, 71 and 45% yields respectively. Conversion of these into the corresponding bromides **182, 183** and **184** was achieved following a general procedure reported by Aizpurua *et al.*,[159] with a slight modification of the amount of $PPh_3.Br_2$ complex used (1.2 equivalents *vs* 1.1 equivalents).

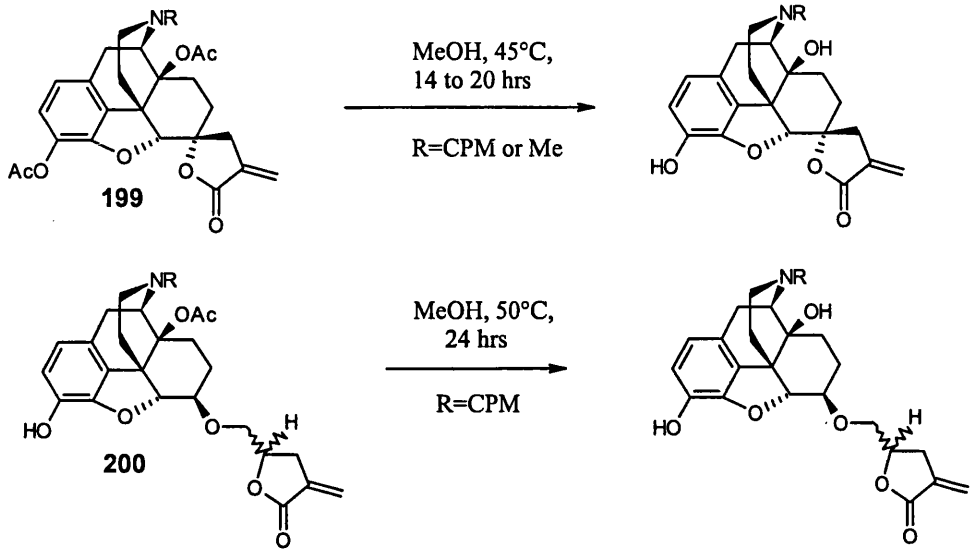
Deprotonation of **178** with three equivalents of sodium hydride and benzylation with **182, 183** and **184** in presence of a catalytic amount of 18-crown-6 gave the desired tetraacetyl N-substituted norBNI-derivatives **197** and **198** (scheme 31). However, it seems that steric hindrance observed with *o*-phthalimidobenzyl bromide precluded nucleophilic attack of **178** in this case.




(a) 4.0 equi. NaH, 0.1 equi. 18-crown-6, 3.0 equi. **182** or **183**, THF, overnight, 70°C

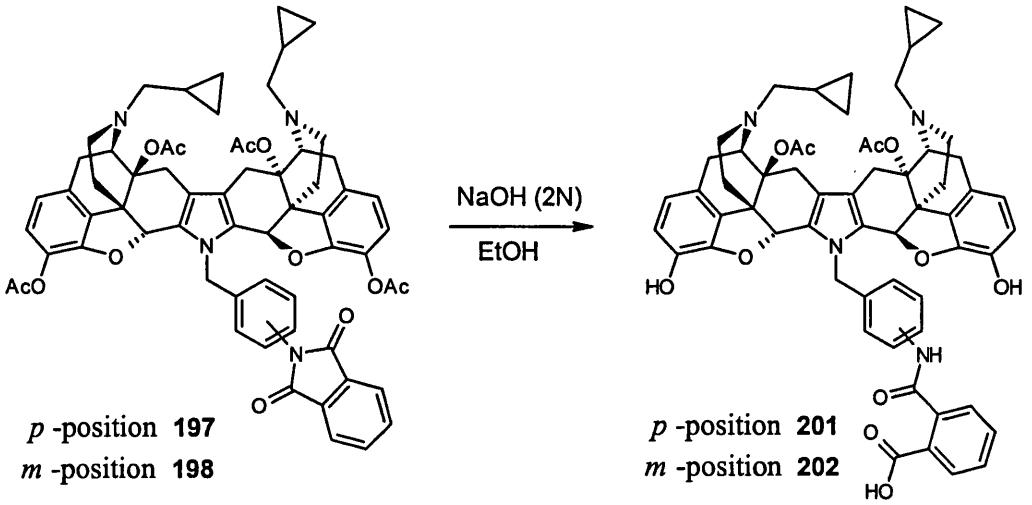
**Scheme 31** Benzylation of **178** with phthalimidobenzyl bromide derivatives

Since the cleavage of acetate protecting groups in the 14-position had been reported in the literature by simply stirring acetyls **199** and **200** in methanol (see scheme 32),[154,155] we attempted to deprotect **197** and **198** using the same procedure, but this resulted only in the recovery of starting materials.




**Scheme 32** Methods reported in the literature for deprotection of 14-OAcetates [154,155]

A solution of the tetraacetyl compounds **197** and **198** in ethanol was then treated with sodium hydroxide (2M aqueous solution) but mass spectrometry suggested this had only resulted in formation of N-substituted phthalamic acids **201** and **202** *via* saponification of the phenolic esters and hydrolysis of the phthalimido-group (see scheme 33).

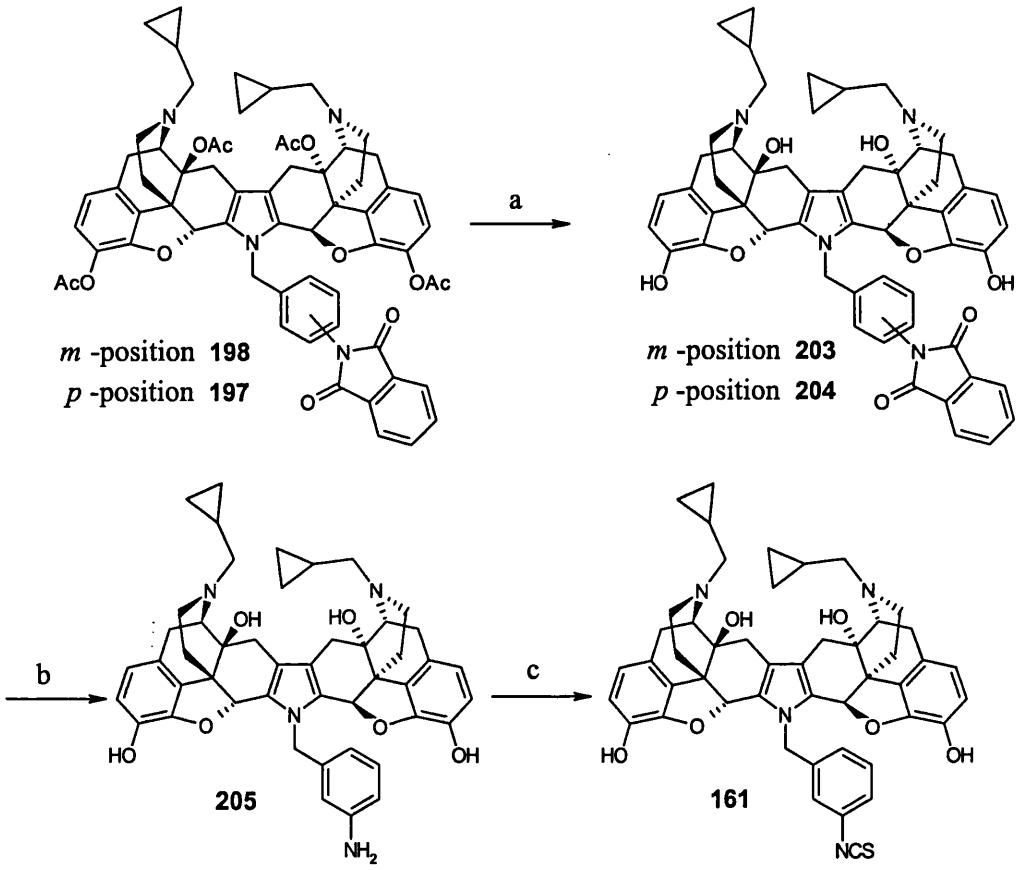



*p* -position **197**
*m* -position **198**

*p* -position **201**
*m* -position **202**

**Scheme 33** Reaction of tetraacetyls **197** and **198** with NaOH (2M)

Though unexpected, ring-opening of phthalimido-protecting groups into stable N-substituted phthalamic acids has been reported in the literature, with subsequent cleavage into the corresponding amines being accomplished using a mild enzymatic approach.[160] Unfortunately, we were unable to purchase the enzyme used in this experiment (*o*-phthalyl amidase). All four esters were eventually cleaved stirring the acetyls overnight in a mixture of methanol/conc. HCl (50/50) at 85°C. This method proved to be somewhat successful for the deprotection of the *m*-derivative **198**, with **203** being isolated in 68% yield (see scheme 34).




(a) conc. HCl/MeOH (50/50), overnight, 85°C; (b) 3 equi. $NH_2NH_2.xH_2O$, 30 hrs, room T°; (c) 6.0 equi. $NaHCO_3$, 1.1 equi $CSCl_2$, $CHCl_3/H_2O$, 2hrs, room T°

**Scheme 34** Deprotection of **197** and **198** and subsequent preparation of **161**

However, the result was much less satisfactory with the *p*-derivative since it afforded the desired product **204** in only 5% yield. The main product was identified as norBNI, which suggests that the bond between the pyrrolic nitrogen and the benzylic carbon is particularly weak when substituted with a *p*-phthalimidobenzyl group. This was corroborated with attempted phthalimido-deprotection of **204**, using 1.2 equivalents of hydrazine hydrate, leading exclusively to unsubstituted norBNI **(13)**. This led us to investigate whether the *p*-phthalimidobenzyl group could represent a general protecting group for indolic and pyrrolic nitrogens and this will be discussed in another chapter (see section 2.7).

Deprotection of phthalimide **203** with 3 equivalents of hydrazine hydrate afforded the corresponding aniline **205**, that was subsequently converted into the corresponding isothiocyanate **161**; this was achieved using 6 equivalents of sodium hydrogencarbonate and 1.1 equivalents of freshly distilled thiophosgene according to a similar procedure as employed in section 2.3.2.d for the preparation of **136**.

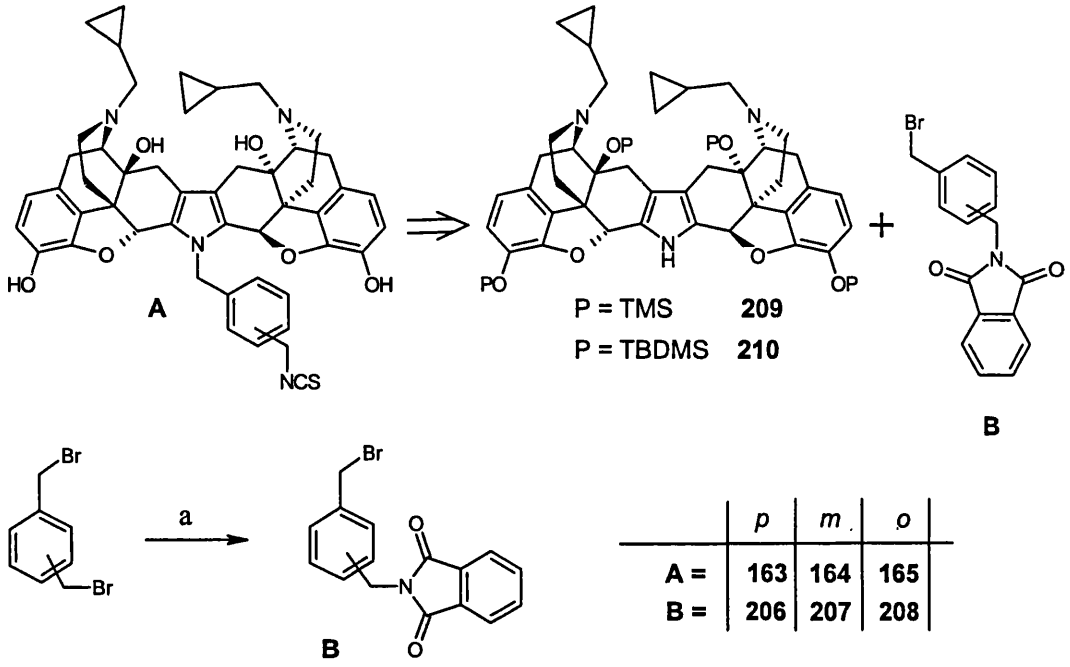
### *2.5.3 Synthesis of compounds 163, 164, and 165*

#### *2.5.3.a Preliminary work*

It was decided to prepare the irreversible ligands **163, 164,** and **165** using an analogous approach to that employed in section 2.5.2, namely *via* benzylation of protected norBNI with benzyl bromide derivatives **206, 207** and **208** (see scheme 35). These were obtained through nucleophilic attack of potassium phthalimide on commercially available dibromoxylenes in presence of 18-crown-6 in refluxing toluene (or in DMF) following a similar procedure reported by Fisher and colleagues.[161]

Given the earlier difficulties encountered with the use of acetate protecting groups for hydroxyls in 14- and 14'-positions, alternative protecting groups were sought that could be both introduced and removed in a facile manner. We instead elected to protect all four hydroxy groups of norBNI **(13)** as silyl ethers. Though known to be extremely labile, we initially opted for trimethylsilyl (TMS) ethers rather than TBDMS ethers because of steric hindrance around the hydroxyls in 14- and 14'-positions. **13** was thus reacted with an excess of both trimethylsilyl chloride and imidazole, which led in quantitative yield to the tetrasilyl ether **209**. Deprotonation of the latter with sodium hydride and subsequent reaction with **206** led to disubstitution

of **209**, most probably as a result of cleavage of TMS ethers at 3- and 3'-positions before subsequent attack of the phenoxide groups.



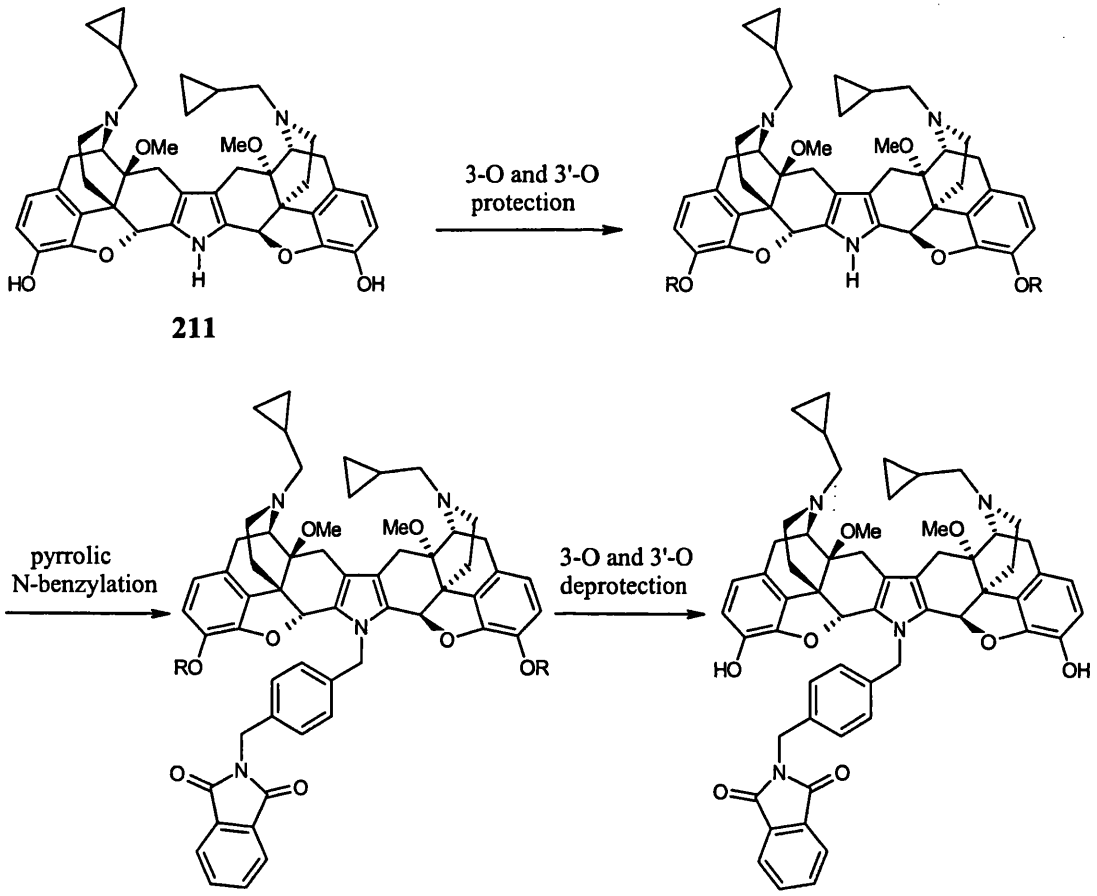

(a) 1.0 equi. potassium phthalimide, 0.1 equi. 18-crown-6, toluene, overnight, reflux

**Scheme 35** Synthetic approach planned for the synthesis of **163**, **164**, and **165**

This led us to protect the hydroxyls of **13** as TBDMS ethers, since these are known to be more stable towards base than TMS ethers.[162] This was achieved in quantitative yield by reacting **13** at room temperature with *tert*-butyldimethylsilyl chloride (1.05 equivalents per hydroxy group) and imidazole (1.1 equivalents per hydroxy group). Since $^1$H NMR spectrometry of the crude material showed the product **210** to be formed cleanly, **210** was not purified but immediately deprotonated with sodium hydride and reacted with **206** according to the general procedure previously described for pyrrolic N-benzylation. After work-up and subsequent deprotection of the silyl ethers with TBAF, the crude product was shown to be very unclean by TLC. Repeated purification by column chromatography failed to afford definite evidence of the desired product; although the main peak (10 times stronger than secondary peaks) on the mass spectrum corresponded to the correct molecular

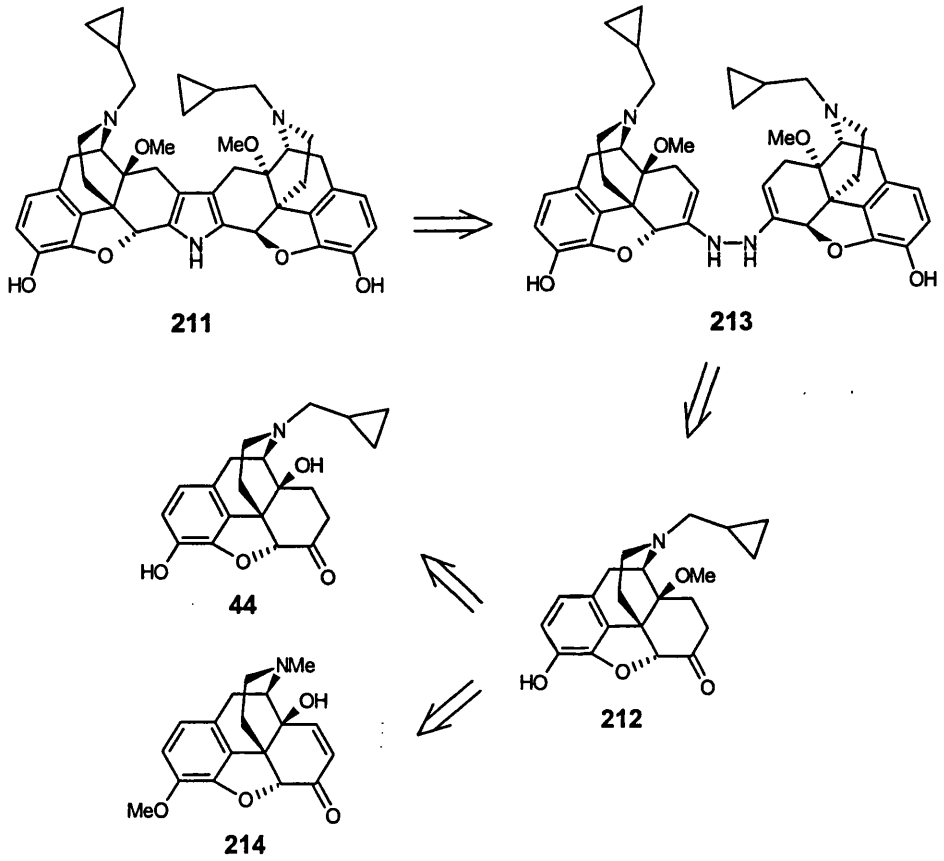
weight, $^1$H-NMR showed that the fraction was a complex mixture of different materials.

Since it had not been possible to prepare the irreversible ligands **163**, **164**, and **165** *via* an easy route utilising simultaneous protection of the phenolic and hydroxy groups of **13**, we investigated preparing the 14,14'-dimethoxy analogue **211.** Methylation of the hydroxyl in 14 position of **44** and its 17-N-allyl derivative has indeed been reported to result in little modification of the pharmacological profile of the parent ligands, while methylation of the hydroxyls in the 14- and 14'-positions of **13** has been shown to result in no modification of κ-affinity.[163] One might thus envisage that the effect of N-benzylation of **211** with **206**, **207** and **208** should be equivalent to that of **13** (scheme 36).




**Scheme 36** Another approach for the preparation of irreversible ligands modelled on norBNI **(13)**

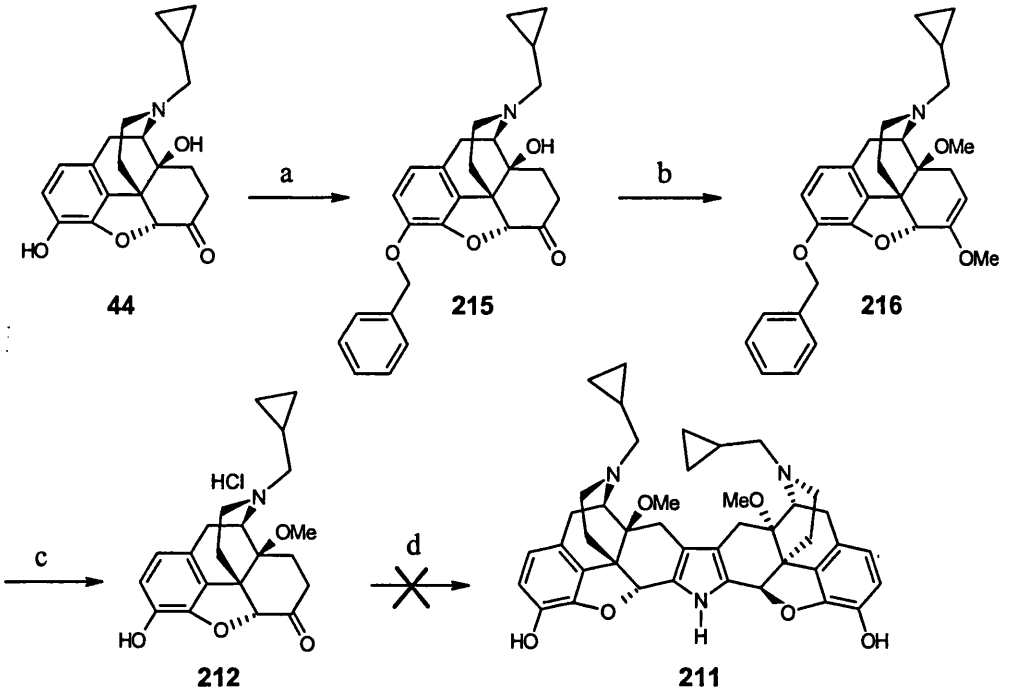
The synthesis of **211** from 14-OMe naltrexone **(212)** has been previously reported by Schmidhammer and associates and involved a two-step synthesis, first reacting **212** with hydrazine hydrate, before heating the product (azine **213**) in presence of methanesulfonic acid (20% yield, see scheme 37).[163] However, it was felt that isolation of the azine intermediate was unnecessary and we instead envisaged preparing **211** using similar reacting conditions as employed for the preparation of norBNI in section 2.4 (scheme 26).




**Scheme 37** Retrosynthetic route for the preparation of **211** [163,164,165]

The preparation of **212** has been reported in the literature starting either from **44** [163,164] or from 14-hydroxycodeinone **(214)**.[165] We opted for the first approach because naltrexone was readily available in our laboratory and also because this method was more straightforward (3 steps instead of 6). These considerations led us to prepare **211** according to the synthetic route presented in scheme 38. Benzylation of naltrexone was achieved using one equivalent of benzyl bromide and an excess of potassium carbonate, which afforded **215** in quantitative yield. The attempted

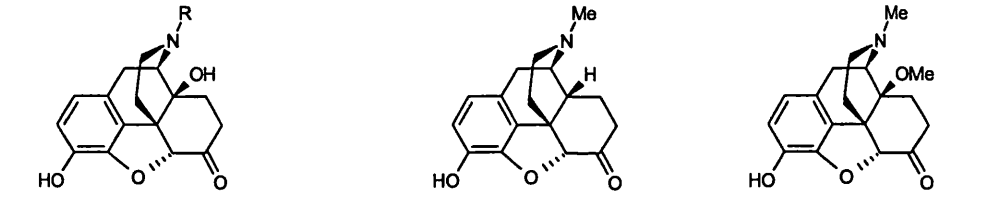
dimethylation of **215** employed a modified version of the procedure used by Schmidhammer *et al.*;[164] thus, 2.1 equivalents of methyl iodide and three equivalents of sodium hydride were used instead of 2.75 equivalents of dimethyl sulfate and an excess of sodium hydride due to the easier removal of excess of methylating agent. The amount of methylating agent was decreased in order to avoid methylation of 17-N that was likely to occur. However, this did not prove successful as the formation of numerous side products was observed and **216** was eventually prepared following Schmidhammer's procedure. It should be noted that monomethylation of **215** at the 14-hydroxyl is not possible because of the propensity of the ketonic group of morphinan-6-ones to exist in the enol form that is susceptible to alkylation.[156] **216** was immediatly refluxed overnight in methanol/conc. HCl (3/2) in accordance with the procedure reported by Schmidhammer's group and this afforded **212** that was purified, carefully dried and converted into its HCl salt (71% overall yield from naltrexone).




(a) 1.3 equi. $K_2CO_3$, 1.0 equi. BnBr, DMF, overnight, room T°; (b) 3.0 equi. NaH, 2.75 equi. dimethyl sulfate, DMF, 2 hrs, 0°C; (c) conc. HCl/MeOH (2/3), overnight, reflux; (d) 0.53 equi. $NH_2NH_2.H_2SO_4$, dry DMF, 6 hrs, 100°C then 0.51 equi. $CH_3SO_3H$, DMSO, 3.5 hrs, 130°C

**Scheme 38** Synthetic route used for the preparation of **211**

Unfortunately, Piloty reaction between the hydrochloride salt of **212** and hydrazine sulfate, following the procedure used in section 2.4, failed to give the desired bivalent ligand **211**. It is noteworthy that similar difficulties were encountered for the reaction of hydrazine sulfate with hydromorphone **(217)** (this will be discussed in section 2.6.2.a). Interestingly, both **212** and **217** lack a hydrogen-bond donor in the 14-position (see figure 10). When the 14-position was occupied by a hydroxyl, a group capable of hydrogen-bond donation, the reaction was found to proceed in good yield (62% yield for reaction with **44** and 75% yield for reaction with **218**, see sections 2.4 and 2.6.2.b respectively). This would suggest that intramolecular hydrogen-bond interactions facilitate the reaction of morphinone-6-ones with hydrazine.




R=CPM, **44**
R=Me, **218**

**217**

**212**

facile pyrrole formation *via* reaction with hydrazine sulfate

low-yielding or failed pyrrole formation *via* reaction with hydrazine sulfate

**Figure 10** Substitution in 14-position and facility of pyrrole formation: a coincidence?

Interestingly, Nagase *et al.* have proposed in their study on dihydromorphinone and related opiates that hydrogen-bond donor/acceptor interactions might partly account for the remarkable enolic character of these ketones.[156] In particular, it seems that the basic nitrogen in 17-position is capable of forming a hydrogen-bond with the hydroxyl in 14-position and that the oxygen atom in 14-position would then remove the axial proton in 7-position, thereby resulting in enolisation of morphinan-6-ones (see figure 11).

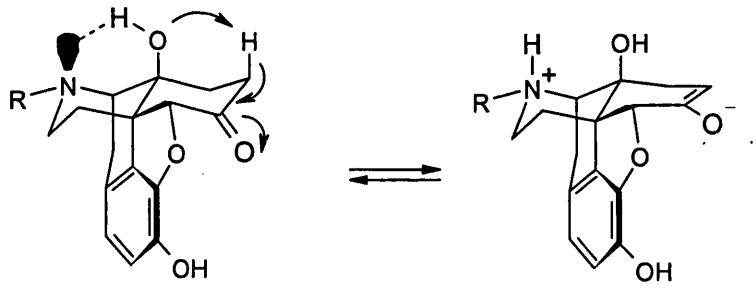



**Figure 11** Importance of hydrogen-bonding in the enolisation of dihydromorphinone and related opiates [156]

The observation that hydromorphone analogues, *ie* morphinans lacking a hydrogen-bond donor in 14-position, require much longer reaction time than equivalent oxymorphones (*ie* with a 14-hydroxyl) to undergo silylation of their enolic group under mild conditions tend to demonstrate the importance of hydrogen-bonding and anchimeric assistance of 17-N and 14-O in the reactivity of these opioids.[156] However, the fact that hydromorphones still undergo silylation indicates that hydrogen-bonding interactions are not a requisite but only one of many factors influencing enolisation. Of greater importance would be the dipolar interaction between the carbonyl group in 6-position and the nearly eclipsed oxygen of the furan ether; since this unfavourable interaction is greatly reduced in the enolic form due to ring flattening, the enolic form is therefore the most thermodynamically favoured.[156]

Since the nitrogen atom is less electronegative than the oxygen atom, it means that this negative dipolar interaction is less marked for imine derivatives than for the corresponding ketones. It is possible that the strong unfavourable dipolar interaction is a sufficient condition for morphinan-6-ones to adopt the enol form but not for an imine to adopt the enamine form. In the latter case, another factor might be required, such as the presence of a hydrogen-bond donor in 14-position. The formation of pyrroles *via* the reaction of morphinan-6-ones with hydrazine proceeds through an azine intermediate (see figure 12). In the absence of a hydrogen-bond donor in 14-position, it is possible that the azine intermediate would have difficulty tautomerising to its enamine form (this might require higher energy than provided by the reacting conditions), which would then result in the failure to react morphinan-6-ones with hydrazine (see figure 12).

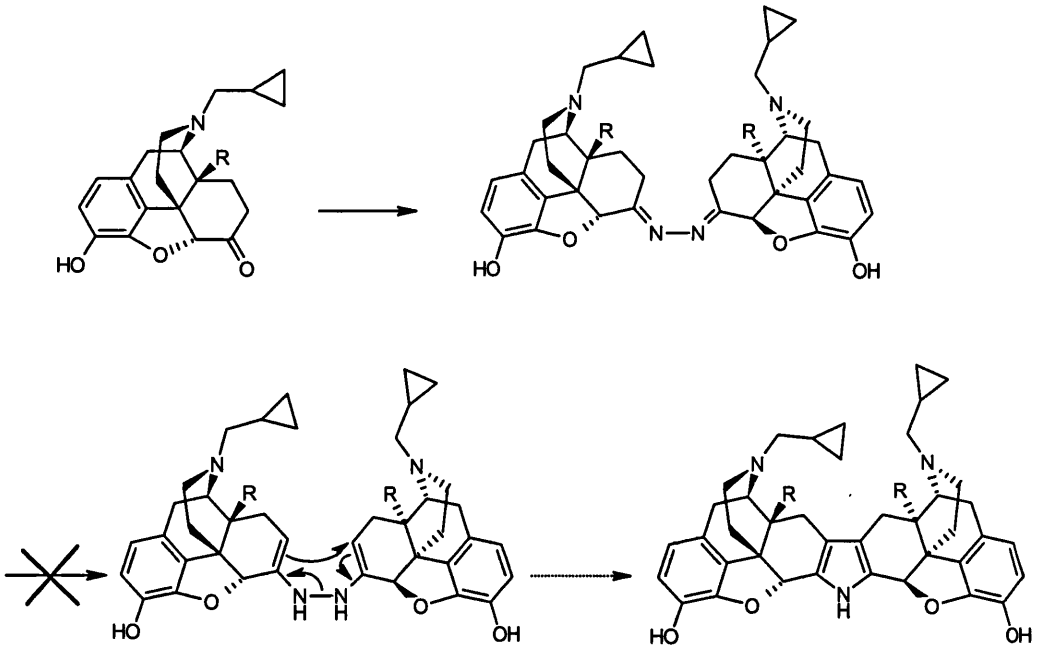


**Figure 12** The formation of pyrroles from the reaction of morphinan-6-ones with hydrazine: azine intermediate

Accordingly, a better approach for the preparation of **211** would be *via* dimethylation of norBNI **(13)**, which initially requires selective protection of the pyrrolic nitrogen and phenolic groups. Such protection had been reported by Schmidhammer and colleagues in their efforts to develop a series of 14-alkoxy-substituted indolomorphinans and involved a MOM-protecting group.[166] This led us to react **13** with 4 equivalents of both sodium hydride and chloromethyl methyl ether, which afforded the tri-MOM-protected bimorphinan **219** (see scheme 39).

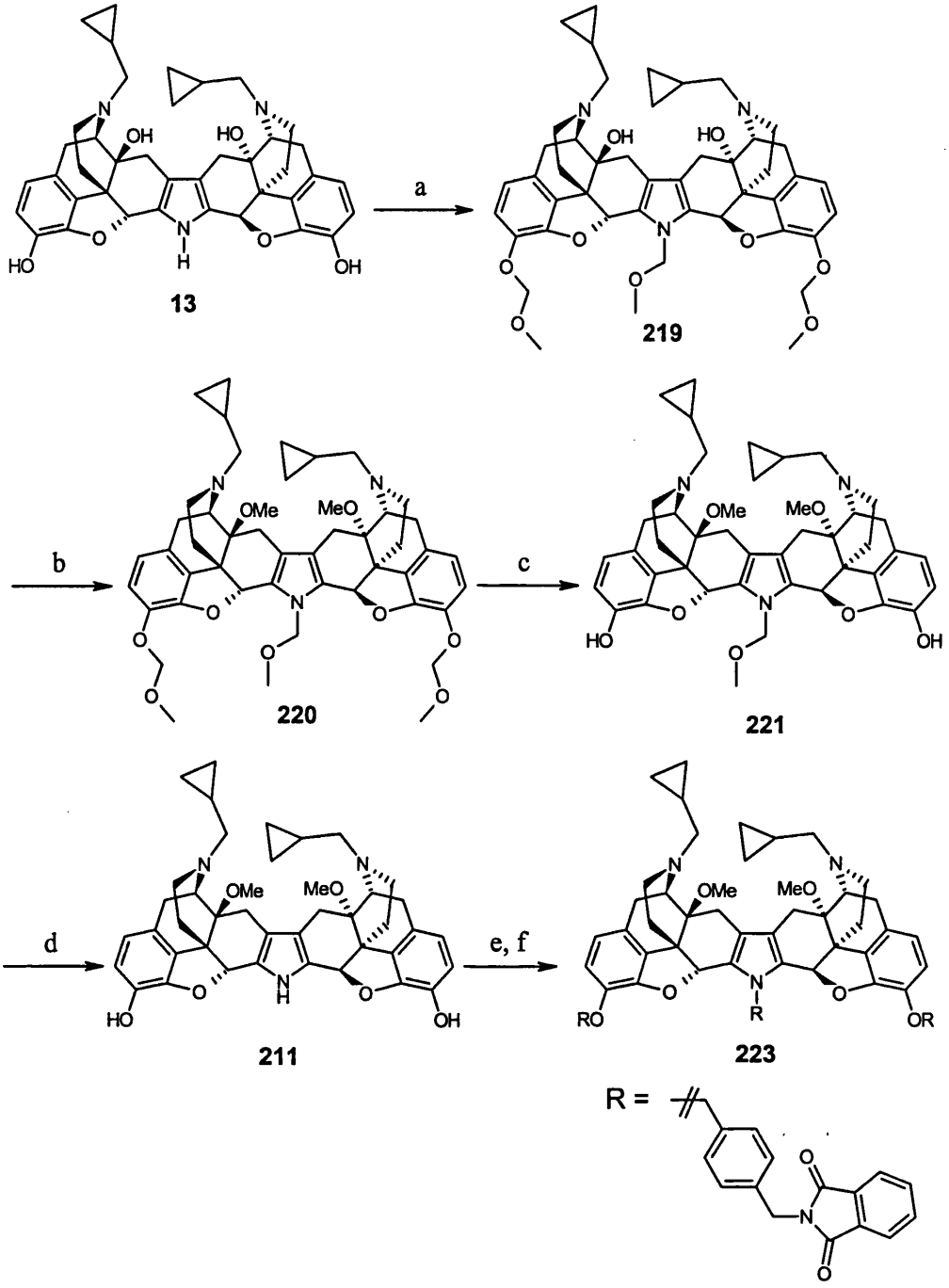
This was dimethylated into **220**, using a similar procedure as employed for the preparation of **216**, *ie* by deprotonating the hydroxy groups with 3 equivalents of sodium hydride before reacting the dianion with an excess of dimethyl sulfate. The yield (22%) was substantially lower than that observed for dimethylation of **215** (72%) and is explained by the presence of monomethylated product and unreacted starting material **219** at the end of the reaction; however, the reaction time could not be extended because of progressive formation of an unidentified side product.

It was not possible to selectively cleave the MOM-protecting group from the pyrrolic nitrogen due to the non-availability of the lone pair of electrons at nitrogen;

indeed, while cleavage of the methoxymethyl group from alcohols is generally achieved under mild conditions, *e.g.* stirring the protected alcohols in methanol in presence of a sulfonic acid, the cleavage from indolic nitrogens is inconsistent and requires much harsher reagents such as $BF_3.Et_2O$.[162] Since Schmidhammer's group had reported that deprotection of the MOM groups from both 3-hydroxyl and indolic-nitrogen could be achieved simultaneously stirring the morphinans in MeOH/1N. HCl under reflux, we also decided to use acidic hydrolysis.[166] We first attempted to remove all three MOM-protecting groups of **220** by stirring overnight at room temperature in a mixture of conc. HCl/MeOH (50/50). However, this afforded **221** still having its pyrrolic nitrogen protected with a MOM group. Complete deprotection into **211** was eventually achieved by treating **221** under similar conditions, but increasing the temperature to 80°C.

Selective reprotection of the phenolic groups of **211** was then required for subsequent benzylation of the pyrrolic nitrogen. Our previous experience with the protection of phenolic groups of norBNI-derived ligands led us to opt for a protecting group that would be stable under strong basic conditions but also very easy to cleave under mild acidic conditions. Since each dimethoxy substitution on the trityl group has been demonstrated to enhance the rate of deprotection by 100-fold, resulting in very facile deprotection, the 4,4'-dimethoxytrityl protecting group appeared a perfect candidate for that aim.[167] **211** was thus reacted with 4,4'-dimethoxytrityl chloride under DMAP-catalysed reacting conditions. Evidence of the formation of the expected intermediate **212** was provided by $^1$H NMR but the product was not purified by column chromatography since its deprotection was likely to occur in presence of silica. **222** was immediately deprotonated with sodium hydride and reacted with **206**. Unfortunately, this did not lead to the desired product but to a main product identified as **223**.

We then envisaged protecting the phenolic groups of **211** with the more stable benzyl group but there was however insufficient amount of material left at this stage to undertake further work.



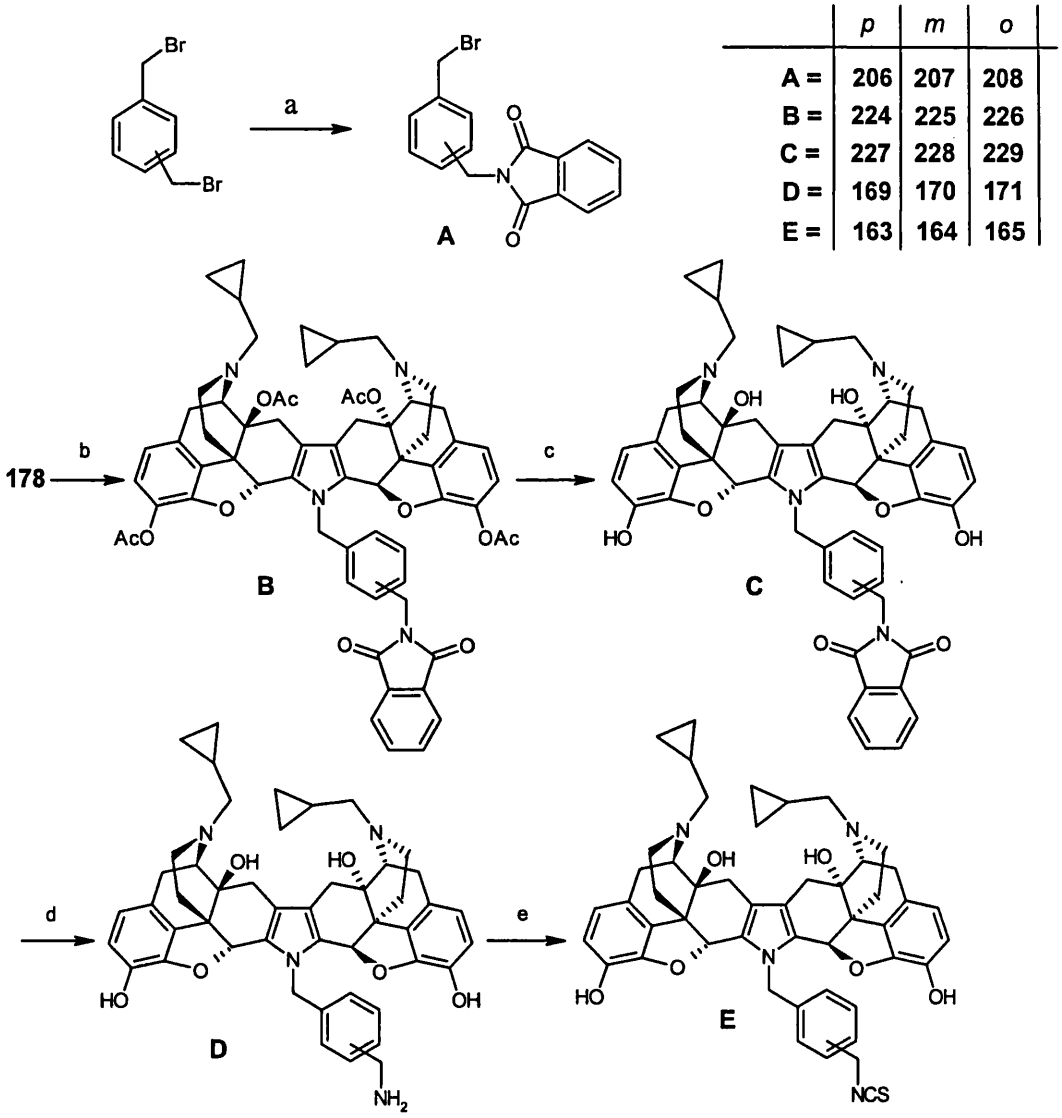

13 219 220 221 211 223

(a) 4.0 equi. NaH, 4.0 equi. chloromethyl methyl ether , dry DMF, 2 hrs, room T°; (b) 3.0 equi. NaH, 2.5 equi. dimethyl sulfate, DMF, 3 hrs, 0°C; (c) conc. HCl/MeOH (1/1), overnight, room T°; (d) conc. HCl/MeOH (1/1), overnight, 80°C; (e) 2.0 equi. 4,4'-dimethoxytrityl chloride, 1.6 equi. DMAP, pyridine, overnight, room T°; (f) 4.1 equi. NaH, 3.0 equi. **206**, dry DMF, overnight, 70°C

**Scheme 39** Preparation of bimorphinan **211** and subsequent pyrrolic N-substitution

*2.5.3.b Synthesis*

Since studies focussing on the protection of 14- and 14'-hydroxyls of **13** did not lead to any useful alternative to the acetate protecting group, we eventually reverted to using acetates in the synthesis of the potential irreversible ligands **163**, **164**, and **165** (see scheme 40).




| | *p* | *m* | *o* |
|---|---|---|---|
| **A =** | **206** | **207** | **208** |
| **B =** | **224** | **225** | **226** |
| **C =** | **227** | **228** | **229** |
| **D =** | **169** | **170** | **171** |
| **E =** | **163** | **164** | **165** |

(a) 1.0 equi. potassium phthalimide, 0.1 equi. 18-crown-6, toluene, overnight, reflux; (b) 4.0 equi. NaH, 0.1 equi. 18-crown-6, 3.0 equi. **206**, **207**, or **208**, dry THF or DMF, overnight, 70°C; (c) conc. HCl/MeOH (1/1), overnight, 85°C; (d) 3 equi. $NH_2NH_2.xH_2O$, 16 to 48 hrs, room T°; (e) 6.0 equi. $NaHCO_3$, 1.1 equi $CSCl_2$, $CHCl_3/H_2O$, 2hrs, room T°

**Scheme 40** Synthetic route used for the synthesis of **163**, **164**, and **165**

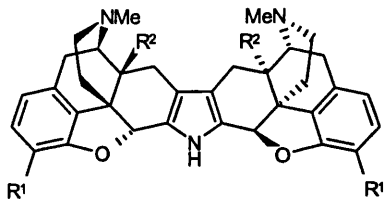
In a similar manner as employed in section 2.5.2, the synthetic route thus involved deprotonation of **178** followed by nucleophilic attack onto benzyl bromides **206**, **207** and **208**, which afforded the desired N-substituted products **224**, **225** and **226**. As expected, attempts to cleave the acetate esters of **224**, stirring in warm methanol, turned out to be unsuccessful. Basic saponification of **224**, **225** and **226** in MeOH/$H_2O$ (9/1) –using potassium carbonate (1.2 to 5 equivalents per acetate group), lithium hydroxide (1.4 equivalents) or concentrated aqueous ammonia– resulted in either recovery or decomposition of the starting materials, with no desired product being isolated. Stirring **224** and an excess of sodium methoxide in methanol at room temperature or at 45°C led again to the recovery of unreacted materials while reduction with diisobutylaluminium hydride (2 equivalents per acetate group) did not afford any useful product. Decomposition of the 14,14'-diacetyl analogue of **224** was also observed when stirring overnight at room temperature in an anhydrous mixture of THF/MeOH (50/50) with 1.4 to 16 equivalents of magnesium. Deprotection of the acetyls **224**, **225** and **226** into **227**, **228** and **229** was eventually accomplished stirring the compounds overnight in a mixture of MeOH/conc. HCl (50/50) at 85°C; it is noteworthy that amines **169** and **171** were also isolated when using such acidic conditions. Treatment of **227**, **228** and **229** with an excess of hydrazine hydrate afforded the desired amines **169**, **170** and **171**, which were finally converted into the corresponding isothiocyanates **163**, **164** and **165**, employing the same procedure as used for the preparation of **161**.

## 2.6 Ligands with mixed profile: μ-agonist/κ-antagonist

### *2.6.1 Rationale and design*

As discussed in the pharmacological section, *in-vivo* biological evaluation of BnorBNI **(152)** showed that this bivalent ligand exhibits μ-opioid receptor agonist activity with modest potency and duration of action when administered subcutaneously (sc), while it displays κ-opioid receptor antagonism with high potency, selectivity and very long duration of action when administered intracerebroventricularly (icv) (see section 3.2). Since there is an interest in developing mixed μ-agonist/κ-antagonist ligands (see section 1.4.2), we decided to attempt to improve the pharmacological profile of **152**, more specifically regarding its μ-agonist effects.

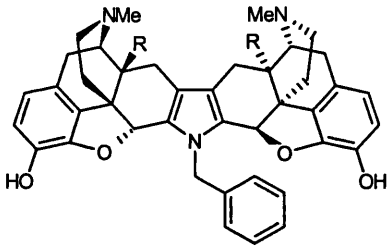
When studying the SAR of BNI-related ligands, Portoghese and associates disclosed three members displaying full agonist activity **(230, 231** and **232)** in the guinea pig ileum (GPI) and mouse vas deferens (MVD) assays; interestingly, all three ligands were N-Me disubstituted derivatives.[102] Further study with **230** in the GPI assay showed that the agonist effects were mediated through the μ-receptor, with similar selectivity likely for the other members.[102] This suggests that the SAR of norBNI derivatives, in particular regarding substitution at N-17 and N-17', follows that displayed by other series of opioids; N-Me substitution typically leads to μ-agonism, while N-CPM substitution generally results in a decrease in μ-efficacy and a more κ-profile. It was therefore of interest to investigate whether similar N-Me disubstitution would optimise the μ-agonist pharmacological profile of BnorBNI; we here investigate the synthesis and biological evaluation of **233** and **234.**




$R^1$= OH, $R^2$=OH **230**

$R^1$= OH, $R^2$= H **231**

$R^1$=$OCH_3$, $R^2$=H **232**




R = OH **233**

R = H **234**

*2.6.2 Synthesis*

*2.6.2.a Synthesis of 233*

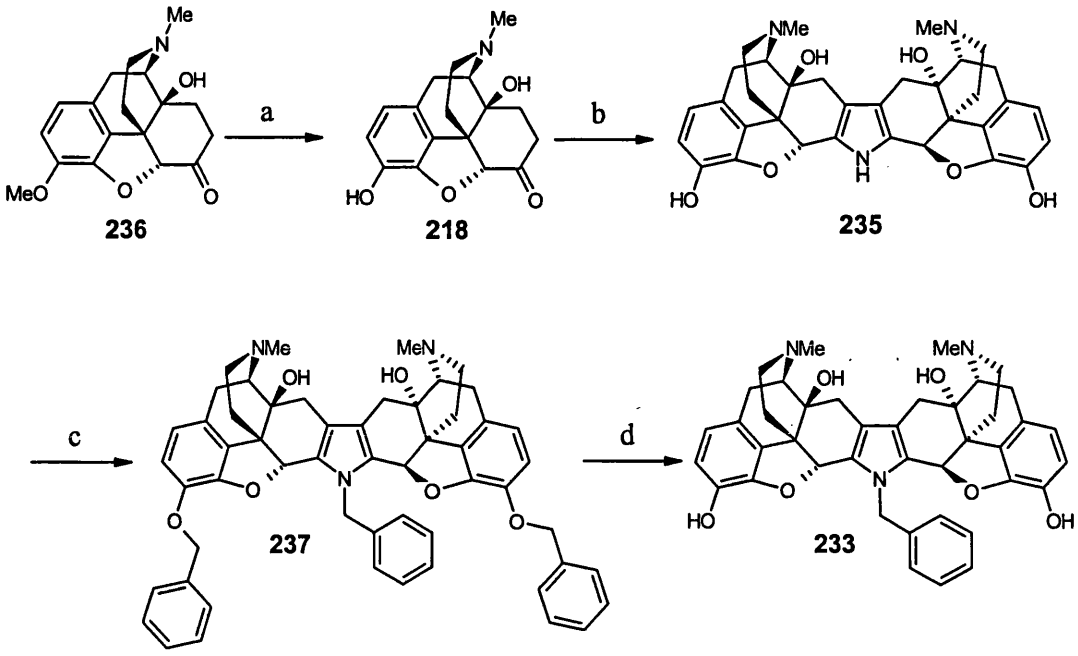
Replacement of N-substituents from the 17-position of morphinans has been reported in the literature and involves alkylation of N-noralkaloid intermediates or quaternisation of the starting tertiary amine followed by dealkylation.[168]

In the first approach, the starting tertiary amine is first reacted either with cyanogen bromide (von Braun reaction) or alkyl chloroformates before cleavage of the cyanamide or carbamate product; the N-noralkaloid intermediate is then alkylated with the appropriate alkyl bromide derivative. However, there were potential problems in applying this method for the conversion of BnorBNI **(152)** into the targeted derivative **233**: reaction of a tertiary amine (constituted of three alkyl groups) with cyanoammonium bromide results indeed in cleavage of the smallest alkyl

bromide.[127] Thus, the method represents an attractive approach for replacing the N-Me group of morphinans, but not for replacing the CPM group of BnorBNI. Of concern was the possible formation of side products arising from cleavage at the 16-position since cyclic amines have been reported to be frequently cleaved through von Braun reaction.[127]

The second approach, *ie* quaternisation of BnorBNI with methyl iodide followed by dealkylation, should lead to the targeted product **233**. However, such a method would present some disadvantages when applied to BnorBNI; firstly, protection and deprotection of the hydroxy groups of BnorBNI was required, which we wished to avoid due to our previous experiences. Also tedious purification was predictable: since BnorBNI is a bivalent ligand, the N-Me disubstituted product **233** would have to be isolated from a mixture likely to contain the N-CPM di-substituted starting material, the mono-converted compound, the products arising from mono/di-Hofmann elimination, amongst others. In the light of these considerations, it seemed inappropriate to synthesise **233** from **152**.

It was instead decided to prepare 17,17'-di-N-Me-substituted norBNI intermediate **235** reported by Portoghese,[102] before subsequent pyrrolic N-benzylation, in a similar approach as used for BnorBNI (see scheme 41). Demethylation of oxycodone **(236)** has been reported under various conditions, *e.g.* heating the morphinan to 110-120°C in aqueous HBr (35% yield) [169] or stirring in aqueous HCl in presence of Pd/C.[170] $BBr_3$ has also been employed for this purpose,[171] but it was believed that better yields would be achieved with $BBr_3$.DMS because of the reduced propensity of $BBr_3$ to complex with the electron-donor groups of oxycodone. We thus decided to utilise this reagent; the experiment was adapted from a general procedure described for dealkylation of aryl ethers [172] and afforded oxymorphone **(218)** in 63% yield. Similar Piloty reaction as used for the preparation of norBNI, starting with the hydrochloride salt of **218** and hydrazine sulfate, afforded the bivalent ligand **235**; this was then deprotonated with sodium hydride and reacted with five equivalents of benzyl bromide, the conditions that had proved successful for the preparation of BnorBNI. This afforded the tri-benzylated product **237**, which was immediately reacted with aqueous HBr (50% in methanol) into the target derivative **233**.




(a) 4.0 equi. $BBr_3$.DMS, dichloroethane, overnight, 65°C; (b) 0.52 equi. $NH_2NH_2.H_2SO_4$, dry DMF, overnight, 105°C then 0.49 equi. $CH_3SO_3H$, DMSO, 4 hrs, 130°C; (c) 10.0 equi. NaH, 0.38 equi. 18-crown-6, 5.1 equi. BnBr, DMF, 24 hrs, room T°; (d) MeOH/conc. HBr (aqueous solution) (1/1), overnight, room T°

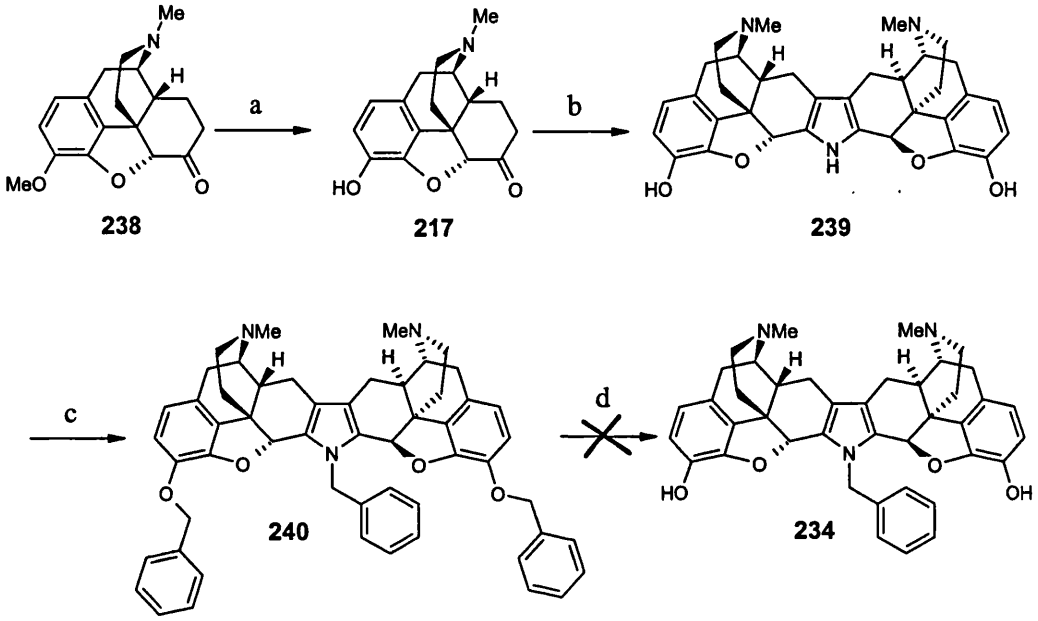
**Scheme 41** Synthetic pathway used for the preparation of **233**

*2.6.2.b Synthesis of 234*

The successful preparation of **233** *via* multiple benzylation and subsequent selective debenzylation prompted us to use the same strategy for the synthesis of **234**, but with hydrocodone **(238)** as the starting material (see scheme 42).

Although demethylation of hydrocodone **(238)** using four equivalents of $BBr_3$.DMS led to the anticipated product hydromorphone **(217)**, the yield turned out to be substantially lower than that observed for the demethylation of oxycodone **(218)** (33% compared to 63%). This was surprising since replacement of the hydroxyl in 14-position with a hydrogen atom was expected to result in reduced complexation with $BBr_3$ and consequently in a higher yield. However, as discussed in section 2.5.3.a, intramolecular hydrogen-bond interactions generally exist between the basic nitrogen in 17-position, the hydroxyl in 14-position and the hydrogen atom in 7-position of morphinan-6-ones;[156] **218** is no exception to that rule and this is demonstrated with

hydromorphone (**217**) being more polar than oxymorphone (**218**) (see $R_f$ values in section 3).[156] Although it is acknowledged that $BBr_3$ was used in excess and as its methyl sulfide complex, it still remains that stronger complexation exists between $BBr_3$ and **238** than between $BBr_3$ and **236**, which might explain why the reaction proceeds better in the latter case. Demethylation of **238** with two equivalents of boron tribromide (from -78°C to room temperature) gave a similar yield (40%). Trimethylsilyl iodide, formed *in-situ* from nucleophilic attack of sodium iodide on trimethylsilyl chloride, was also utilised to see if this would allow a more efficient synthesis of **217**, but this procedure failed to give any demethylated product.




(a) 4.0 equi. $BBr_3$.DMS, dichloroethane, overnight, 65°C; (b) 0.52 equi. $NH_2NH_2.H_2SO_4$, dry DMF, overnight, 105°C then 0.49 equi. $CH_3SO_3H$, DMSO, 4 hrs, 130°C; (c) 10.0 equi. NaH, 0.38 equi. 18-crown-6, 5.1 equi. BnBr, DMF, 24 hrs, room T°; (d) MeOH/HBr (in AcOH) (1/1), overnight, room T°

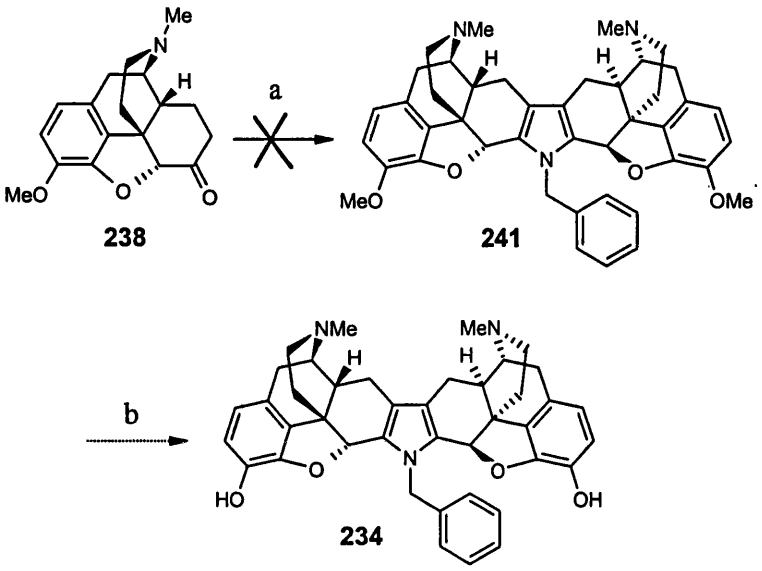
**Scheme 42** Synthetic route planned for the preparation of **234**

Although preparation of the bivalent ligand **239** from **217** has been reported by Portoghese *et al.* using N-aminosuccinimide hydrochloride,[173] we instead decided to use 1.1 equivalents of hydrazine sulfate in a similar way as used for the preparation of **235**. The desired product **239** was isolated in 35% yield; again, the yield was lower

than that obtained with the 14-OH analogue **235**, which is in line with our previous observation that pyrrole formation *via* reaction between hydrazine and morphinan-6-ones proceeds in much better yield when the 14-position is occupied by a hydrogen-bond donor (see section 2.5.3.a).

Our greatest surprise came however when reacting deprotonated **239** with five equivalents of benzyl bromide. We indeed believed that the reaction would proceed better than when starting with **235** because of the lack of hydroxy groups in 14- and 14'-positions. However, this proved not to be the case and the desired product **240** was obtained in very low yield (19 %). Moreover, repeating the reaction several times showed the result not to be reproducible, with highly-benzylated species being routinely formed; unfortunately, it was not possible to characterise these products. This led us to change the reacting conditions, including reducing the amount of sodium hydride and/or benzyl bromide, replacing sodium hydride with potassium *tert*-butoxide or sodium hydroxide. According to mass spectrometry, use of 4 equivalents of potassium hydroxide and 3.5 equivalents of benzyl bromide afforded a complex mixture of penta-, tetra- and tribenzylated derivatives, while hexa-, penta- and tetrabenzylated products were obtained when using 3.1 equivalents of *tert*-butoxide and 3.2 equivalents of benzyl bromide. In both cases, no starting material was isolated, suggesting that some decomposition had occurred during the reaction. Accepting the low yield of the original procedure, **240** was then treated with HBr in acetic acid in order to cleave the phenolic benzyl ethers. Unfortunately, no product was obtained and there was insufficient amount of material left to try any other method of debenzylation.

This urged us to explore another approach for the preparation of **234**, namely the two-step synthetic pathway presented in scheme 43. The first step involved a Piloty reaction between hydrocodone **(238)** and benzylhydrazine dihydrochloride; although reaction of morphinan-6-ones with substituted hydrazine seemed to prove difficult in our hands (for example, such a procedure afforded BnorBNI in only 1% yield, see section 2.4.2), we still hoped the reaction would work in this case since Schmidhammer and co-workers had reported that stirring a mixture of hydrocodone **(238)** and N-methylhydrazine sulfate in acetic acid for 3 hours at room temperature led smoothly to the desired product.[174]



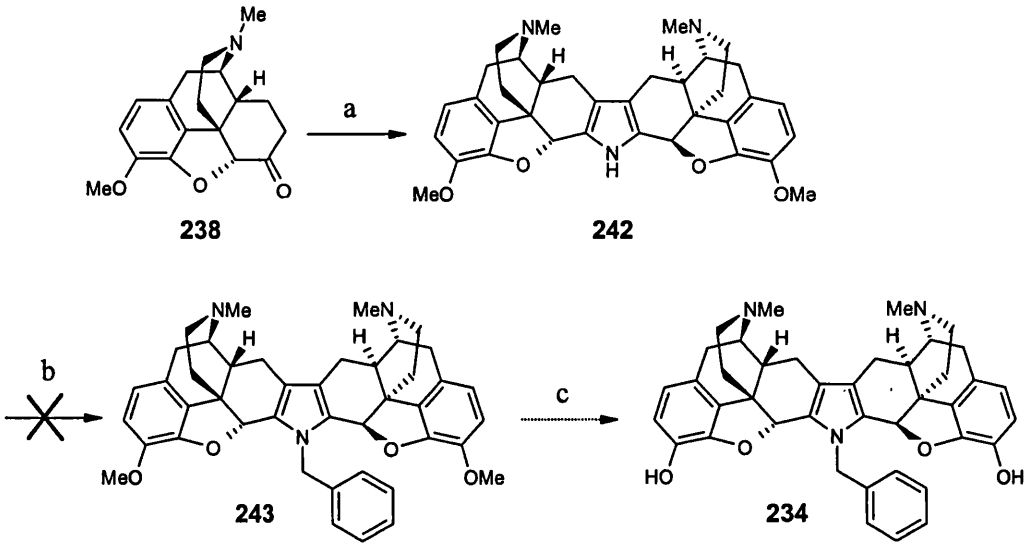

(a) 0.52 equi. $BnNHNH_2.2HCl$, dry DMF, overnight, 105°C then 0.49 equi. $CH_3SO_3H$, DMSO, 4 hrs, 130°C; (b) 8.0 equi. $BBr_3$.DMS, dichloroethane, overnight, 65°C

**Scheme 43** Alternative approach for the preparation of **234** (*via* Piloty reaction between **238** and benzylhydrazine)

However, reacting the HCl salt of hydrocodone **(238)** with benzylhydrazine dihydrochloride in an analogous manner as usually employed within our group for pyrrole formation, *ie* stirring first in DMF at 100°C then in DMSO and methanesulfonic acid at 130°C, failed in giving any desired product **241**. Modification of the reacting conditions, namely stirring overnight the free base or the salt of both hydrocodone and benzylhydrazine in refluxing ethanol in presence of molecular sieves before proceeding as described earlier for the second stage, did not afford the desired product. Finally, stirring hydrocodone **(238)** and benzylhydrazine in acetic acid, following an equivalent procedure to that employed by Schmidhammer and associates, also proved unsuccessful.[174] The reaction mixture was then stirred for one hour at 70°C, but this led to the same conclusion.

Since reaction of morphinan-6-ones with substituted hydrazine had not proved successful in our hands, we instead planned to react **238** with unsubstituted hydrazine before subsequent pyrrolic N-benzylation and 3,3'-demethylation (see scheme 44). This new approach also offered the advantage that both phenolic groups of **242** were

"protected" during pyrrolic N-benzylation, which should reduce extra-benzylation observed when reacting the 3,3'-dihydroxyl derivative **239**.




(a) 0.50 equi. $NH_2NH_2.H_2SO_4$, dry DMF, overnight, 105°C then 0.51 equi. $CH_3SO_3H$, DMSO, 4 hrs, 130°C; (b) lithium diisopropylamide (from 1.05 equivalents to 1.5 equivalents), 0.1 equivalent 18-crown-6, benzyl bromide (from 1.1 equivalents to 3.3 equivalents), dry THF, overnight, reflux; (c) 8.0 equi. $BBr_3$.DMS, dichloroethane, overnight, 65°C

**Scheme 44** Alternative approach for the preparation of **234** (*via* Piloty reaction between **238** and hydrazine)

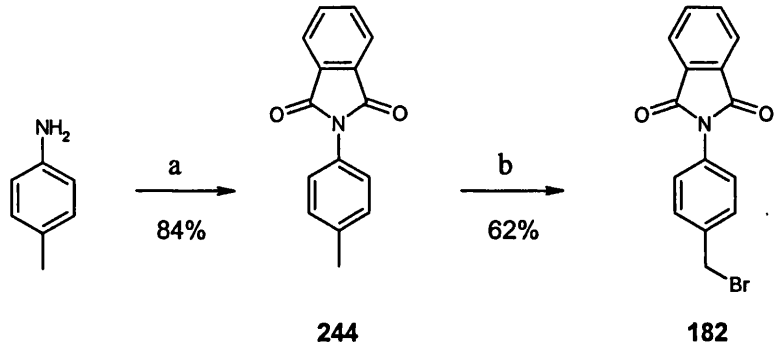
Condensation of hydrocodone hydrochloride with hydrazine sulfate followed by acid-catalysed cyclisation, using an equivalent procedure to that employed for the preparation of norBNI **(13)**, led to the desired product **242** in 71% yield. This suggests that substitution of hydrazine prior to its reaction with morphinan-6-ones is a critical impediment to the success of the reaction; it is possible that steric hindrance inherent to the benzyl substituent shifts the azine intermediate to a conformation unfavourable to subsequent electron transfer.

We then decided to use lithium diisopropylamide for the deprotonation of **242** since it is a hindered base, which might reduce the number of deprotonated sites and result in selective benzylation of the pyrrolic nitrogen. Moreover, using freshly-titrated LDA solution appeared particularly convenient for our purpose, for the scale

we were working on was quite small (less than 0.5 mmol). Unfortunately, all attempts to benzylate **242** using lithium diisopropylamide (from 1.05 equivalents to 1.5 equivalents) and benzyl bromide (from 1.1 equivalents to 3.3 equivalents) led to the decomposition and/or recovery of **242**, with no useful product **243** isolated.

## 2.7 Studies towards a new protecting group for pyrrolic and indolic nitrogens

Since it was found in section 2.5 that N-substitution of norBNI **(13)** with a *p*-phthalimidobenzyl group did not survive acidic or hydrazinolytic environment, we decided to investigate whether such a group could find application as a protecting group for pyrrolic and indolic nitrogens. Should the *p*-phthalimidobenzyl group be envisaged as a protecting group, a higher-yielding approach for its preparation had also to be achieved. This led us to plan the synthesis of **182** *via* the two-step route presented in scheme 45.



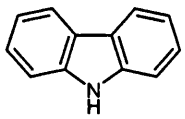

**244** **182**

(a) 1.0 equi. phthalic anhydride, AcOH, 2 hrs, reflux
(b) 3.0 equi. $NaBrO_3$, 3.0 equi. $NaHSO_3$, EtOAc/$H_2O$, 6 hrs, room T°

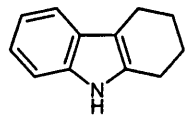
**Scheme 45** Two-step synthesis of **182**

Reaction of *p*-toluidine with one equivalent of phthalic anhydride in refluxing acetic acid led to the protected intermediate **244** in 84% yield. With greater and greater environmental concern, new procedures using environmentally-friendly solvents or generating bromine *in-situ* have recently appeared for benzylic brominations,[175,176] which led us to brominate **244** using a mixture of sodium bromate/sodium hydrogensulfite in a similar way as reported by Kikuchi and co-workers.[176] This led to **182** in 62% yield (52% overall yield from *p*-toluidine).

We then evaluated the use of the *p*-phthalimidobenzyl group for the protection of indolic nitrogens. To that end, we reacted **182** with the conjugate base of carbazole **(245)** and tetrahydrocarbazole **(246)** according to the same procedure as employed for benzylation of **178**.

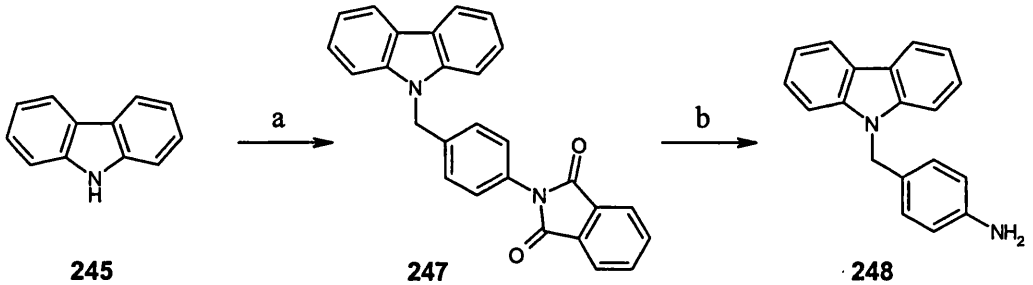


**245**



**246**

In both cases, monitoring of the reaction by TLC showed the reaction mixture to be surprisingly messy; replacing sodium hydride with potassium *tert*-butoxide or a milder base such as potassium carbonate did not result in cleaner reactions. It is unclear whether the product and/or starting materials decomposed during the reaction or during the purification; of additional concern, is the fact that both commercially available and freshly ordered carbazole and tetrahydrocarbazole gave similar messy TLCs despite getting very clean NMR spectra. Because of complex purification, the protection of tetrahydrocarbazole with **182** was abandoned, while indolic N-substitution of carbazole afforded the desired product **247** in modest yield (37%) (scheme 46). Deprotection of **247** with three equivalents of hydrazine hydrate also proved to be messy when monitored by TLC but the fact that amine **248** was isolated suggested that the deprotection was not proceeding in an analogous manner to that with norBNI **(13)**.

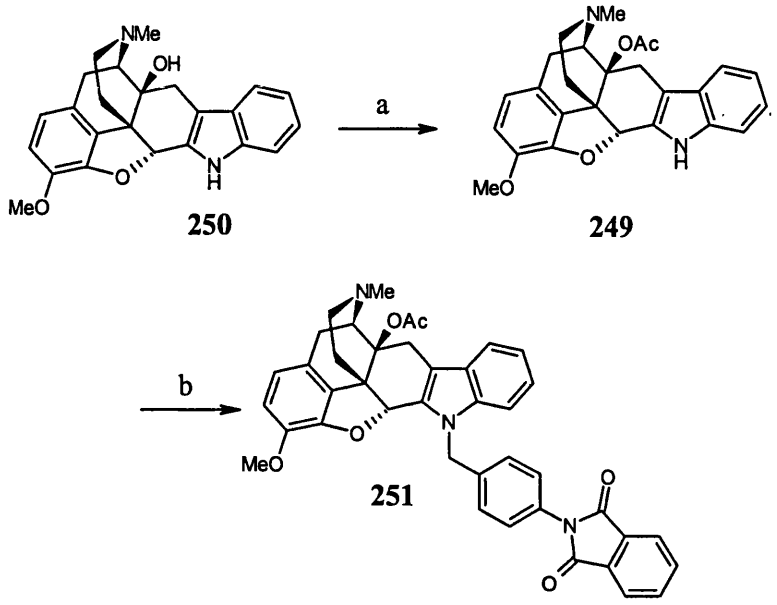



**245** **247** **248**

(a) 2.0 equi. NaH, 1.1 equi. **182**, 0.1 equi. 15-crown-5, dry DMF, overnight, 70°C;
(b) 3.0 equi. $NH_2NH_2.xH_2O$, EtOH, 2 days, room T°

**Scheme 46** Protection and deprotection of **245** with a *p*-phthalimidobenzyl group

Since it was clear that carbazole and tetrahydrocarbazole did not represent ideal candidates for the evaluation of the *p*-phthalimidobenzyl group as a nitrogen-protecting group, we further conducted our study with indolomorphinan **249** (scheme 47); this was obtained from esterification of readily available **250** with acetic anhydride, in a similar way as employed for the preparation of **178**.




(a) acetic anhydride, 3 hrs, 100°C; (b) 4.0 equi. NaH, 0.1 equi. 15-crown-5, 3.0 equi. **182**, dry DMF, overnight, 70°C

**Scheme 47** Protection of **249** with a *p*-phthalimidobenzyl group

Deprotonation of **249** with an excess of sodium hydride followed by nucleophilic attack on **182** gave the desired N-substituted product **251**. **251** was subsequently treated with either a mixture of MeOH/conc. HCl (50/50) at 85°C or with 3 equivalents of hydrazine hydrate at room temperature; in both cases, TLC showed consumption of the starting material with neither **249** or **250** being formed. In the light of these experiments, it seems that the *p*-phthalimidobenzyl group cannot be used as a general protecting group for indolic or pyrrolic nitrogens.

# 3. PHARMACOLOGICAL EVALUATION

## 3.1 Methods

The initial pharmacological evaluation of all ligands was performed by NIDA-OTDP through a contract to SRI or by Dr. John R. Traynor and colleagues; all ligands were evaluated in binding assays, measuring the affinity at each receptor type, and *in-vitro* ([$^{35}$S]GTPγS assay), measuring the antagonist and agonist potency (and efficacy) at each receptor. In some cases, the pharmacological profile of the test compound was also investigated *in-vivo*. At the time of submission, only pharmacological data related to compounds **13**, **152**, **233**, **235**, **50** and **51** were available.

### *3.1.1 Binding assays*

The identification and purification of homogenous populations of opioid receptors has allowed the development of assays that measure the amount of radiolabeled ligand bound to these receptors. By determining the concentration ($IC_{50}$) of unlabeled test compound required to displace 50% of radiolabeled ligand from the receptor, one can calculate the affinity of the test compound for this receptor using the following formula:[177]

$$K_i = \frac{IC_{50}}{1 + \frac{[D]}{K_D}}$$

where, $K_i$ = dissociation constant of test compound
[D] = concentration of radiolabeled ligand
$K_D$ = dissociation constant of radiolabeled ligand

### *3.1.2 Functional assays*

In the present project, *in-vitro* evaluation of the test compounds was based on stimulation of opioid receptor-mediated binding of the GTP analogue guanosine-5'-*O*-(3-[$^{35}$S]thio)triphosphate ([$^{35}$S]GTPγS) to human κ, μ and δ-receptors transfected into Chinese hamster ovary cells (NIDA-OTDP) or rat μ and δ-receptors transfected into C6 cells (Traynor and colleagues).[178,179] Thus, dose-response curves of [$^{35}$S]GTPγS binding mediated by selective agonists DAMGO (for μ), SNC80 (for δ, NIDA-OTDP), DPDPE (for δ, Traynor and colleagues) and U69593 (for κ) were recorded in presence or absence of the test compound.

Antagonist potency was determined from the concentration of the test compound required to lower [$^{35}$S]GTPγS binding by 50% according to the formula:

Ke = [antagonist]/(dose ratio –1), where dose ratio corresponds to the ratio between [antagonist] and the concentration of the radiolabeled ligand required to get 50% of maximal [$^{35}$S]GTPγS binding.

Agonist potency at a receptor type was determined from the concentration ($EC_{50}$) of the test compound required to get 50% of the [$^{35}$S]GTPγS binding value obtained with the standard agonist. Relative efficacy of agonist test compounds at a receptor type was determined by the percentage of maximal stimulation of [$^{35}$S]GTPγS binding obtained with the test ligand compared to that observed with the full agonist selective to that receptor.

### *3.1.3 In-vivo assays*

*In-vivo* assays are often based upon response of rodents to a wide range of nociceptive stimuli including temperature, chemical irritants or electric shocks. *In-vivo* pharmacological evaluation of the ligands synthesised in the present project was achieved using the warm-water tail withdrawal assay, in which the temperature was 50°C.[180]

## 3.2 Pharmacological evaluation of 13, 152, 233 and 235

**13**, **152**, **233** and **235** were evaluated in opioid binding assays and *in-vitro* stimulation of [$^{35}$S]GTPγS binding with BnorBNI **(152)** further evaluted *in-vivo* in the tail withdrawal assay (in mice).

The binding affinities are reported in table 3 and showed subnanomolar affinity of both **13** and **152** for κ-receptors with modest selectivity over μ and δ (≤ 15-fold). When compared to **13**, **152** had 8-fold lower μ-affinity than norBNI and as a result slightly improved κ/μ selectivity. Although Takemori *et al.* have reported similar low κ-selectivity for the closely related analogue **28**,[81] the low selectivity observed with norBNI **(13)** is surprising and is in disagreement with previous reports (around 160-fold κ-selectivity over both μ and δ);[81] it is unclear why the results are divergent but it is noteworthy that the methods used by Takemori *et al.* differed from that used by our collaborators (different tissue and different radiolabeled ligands). The N-Me analogues **235** and **233** also showed modest κ-selectivity broadly in line with that seen for **13** and **152**. The replacement of the N-CPM substituents by N-Me resulted in similar decreases in κ and δ-affinity of around an order of magnitude, but

in contrast the effect on μ-affinity was not consistent. While **235** exhibited 50-fold lower μ-affinity than **13**, replacement of the N-CPM group of **152** resulted in slightly higher μ-affinity for **233**.

| | $K_i$ (nM) | | | Selectivity | |
|---|---|---|---|---|---|
| | μ | δ | κ | κ/μ | κ/δ |
| **13** | 1.2 ± 0.2 | 5.8 ± 0.7 | 0.4 ± 0.1 | 3 | 15 |
| **152** | 10.0 ± 2.5 | 8.6 ± 0.7 | 0.7 ± 0.1 | 14 | 12 |
| **235** | 63.6 ± 39.1 | 98.2 ± 25.3 | 7.7 ± 1.0 | 8 | 13 |
| **233** | 6.4 ± 1.1 | 207 ± 96 | 24.9 ± 5.6 | 0.3 | 8 |

Values are from 3 separate experiments, each performed in duplicate
Radiolabeled ligand is nonselective antagonist [$^3$H]diprenorphine

**Table 3** Affinities in opioid receptor displacement binding assays

In the *in-vitro* functional assay, **152** exhibited partial μ- and κ-agonist activity of modest and low potency respectively (see table 4); its agonists effects showed a 10-fold μ/κ selectivity and reached respectively 38% and 29% of maximal effect compared with the full agonists at each receptor. **13** showed no opioid agonist activity at any receptor, which is in agreement with literature reports.[81]

| | $EC_{50}$ (nM) and % Stimulation | | | | |
|---|---|---|---|---|---|
| | [$^3$H]DAMGO - μ | % Stim | [$^3$H]SNC80 - δ | [$^3$H]U69593 - κ | % Stim |
| **13** | -[a] | - | -[a] | -[a] | - |
| **152** | 187[b] | 38 | -[a] | 1906[c] | 29 |
| **235** | 1388 ± 370 | 66 | -[a] | -[a] | - |
| **233** | 526 ± 279 | 54 | -[a] | -[a] | - |

Values are from 3 separate experiments; [a]: no stimulation up to 10,000 nM; [b]: 95% CI, 42-844 nM. ; [c]: 95% CI, 269-13490 nM.

**Table 4** Opioid agonist effects measured by the [$^{35}$S]GTPγS assay

Both **235** and **233** possessed weak μ-agonist effects with no detectable agonism at κ- and δ-receptors. Both compounds showed higher efficacy than that exhibited by the corresponding N-CPM derivatives, which is in agreement with general SAR studies related to 17-N substitution of morphine derivatives (see section 2.6.1). It is noteworthy that while pyrrolic benzylation of **13** to **152** had resulted in an increase in μ-efficacy, equivalent benzylation of **235** to **233** had resulted in improved μ-potency but slightly reduced μ-efficacy.

As the compounds displayed little efficacy at opioid receptors, they were evaluated as opioid antagonists, the exception being **235** and **233** at μ-receptors where they had too high efficacy. In the opioid antagonist functional assay, **152** exhibited potent κ-antagonism with a 50-fold κ/δ and 100-fold κ/μ selectivity (table 5). In both cases, the selectivity was similar or higher than that showed by norBNI **(13)** (47 and 22-fold respectively). Both N-Me analogues **235** and **233** were weak antagonists at κ-receptors, with a 2-3 order of magnitude lower potency than the corresponding N-CPM derivatives **13** and **152**.

| | $K_e$ (nM) | | | Selectivity | |
|---|---|---|---|---|---|
| | [$^3$H]DAMGO - μ | [$^3$H]SNC80 - δ | [$^3$H]U69593 - κ | κ/μ | κ/δ |
| **13** | 2.38 ± 0.58 | 5.17 ± 0.73 | 0.11 ± 0.11 | 22 | 47 |
| **152** | 25.5 ± 2.3 | 13.3 ± 4.5 | 0.26 ± 0.09 | 98 | 51 |
| **235** | NT | NT | 27.0 ± 4.3 | - | - |
| **233** | NT | NT | 311 ± 30 | - | - |

Values are from three separate experiments; NT : not tested

**Table 5** Opioid receptor antagonist activity in the [$^{35}$S]GTPγS assay

Replacement of the N-CPM substituents with N-Me has thus resulted in increased μ-agonist efficacy of both **13** and **152**; of concomitant effect, was the huge decrease in κ-antagonist potency observed upon such modification. It is difficult to compare this effect with previously reported similar replacement of 17-N-CPM group of GNTI **(11)** and NTI **(150)**. While such modification has been reported to result in

loss of selectivity and potency in the δ-antagonist activity of **150**, with simultaneous appearance of δ-agonism, the N-Me derivative of **11** exhibited no agonist activity but was a κ-antagonist with decreased κ-selectivity and potency compared to **11**.[88,181]

The pharmacological profile of BnorBNI **(152)** was further investigated *in-vivo*; its agonist and antagonists effects on the dose-response curve of the selective κ-agonist U69593 were evaluated with the drug being either administered sc or icv. The results are presented in tables 6 and 7 respectively (negative shift values reflect a leftward shift on the dose-response curve of the agonist, while positive values reflect a rightward shift).

| Treatment conditions applied to U69593 | $EC_{50}$ mg/kg | Fold shift | Shift significance p value [b] |
|---|---|---|---|
| U69593 | | | |
| + vehicle at –1h [a] | 5.2 | — | — |
| + 10 mg/kg BnorBNI at –1h | 2.0 | -2.56 | 0.0002 |
| + 10 mg/kg BnorBNI at –3h | 2.1 | -2.55 | 0.0145 |
| + 10 mg/kg BnorBNI at –18h | 9.0 | 1.73 | n.s. |
| + 10 mg/kg BnorBNI at –24h | 4.4 | -1.17 | n.s. |
| + 32 mg/kg BnorBNI at –24h | 5.7 | 1.09 | n.s. |
| + 10 mg/kg BnorBNI at –48h | 9.9 | 1.90 | n.s. |
| | | | |
| + norBNI vehicle at –1h | 5.5 | — | — |
| + 10 mg/kg norBNI at –24h | 8.1 | 1.47 | n.s. |
| + 32 mg/kg norBNI at –24h | 22.7 | 4.12 | 0.0003 |

[a] vehicle is 10% DMSO in normal saline

[b] n.s. : not significant; shift significance represent the significance of difference between vehicle and drug curves

**Table 6** Effect of sc administered antagonists on the dose-effect curve of U69593 in the warm water tail withdrawal assay (U69593 administered sc)

| Treatment conditions | $EC_{50}$ mg/kg | Fold shift | Shift significance p value [a] |
|---|---|---|---|
| U69593 | | | |
| + vehicle at –1h [b] | 5.2 | — | — |
| + 10 nmol BnorBNI at –1h | 26.3 | 5.04 | <0.0001 |
| + 10 nmol BnorBNI at –24h | 26.3 | 5.04 | 0.0003 |
| + 10 nmol BnorBNI at –48h | 74.2 | 14.22 | <0.0001 |
| + 10 nmol BnorBNI at –168h | 37.0 | 7.09 | <0.0001 |
| + 32 nmol BnorBNI at –24h | — [c] | — | <0.0003 |
| | | | |
| + 10 nmol norBNI at –24h | 31.8 | 6.10 | <0.0001 |
| + 32 nmol norBNI at –24h | — [c] | — | <0.0001 |
| | | | |
| Morphine | | | <0.0001 |
| + 10 nmol BnorBNI at –1h | 5.4 | 2.00 | 0.3415 |
| SNC80 [d] | | | |
| + 10 nmol BnorBNI at –1h | 4.6 | -1.41 | 0.1563 |

[a] shift significance represent the significance of difference between vehicle and drug curves; [b] vehicle is 10% DMSO in normal saline ; [c] $EC_{50}$ could not be calculated because the curve was shifted beyond the agonist dose range; [d] SNC80 was not a full agonist

**Table 7** Effect of centrally (icv) administered antagonists on the dose-effect curve in the warm water tail withdrawal assay (U69593 administered sc)

Subcutaneous administration of BnorBNI **(152)** (10 mg/kg) at pretreatment times up to 3 hours before U69593 administration sc produced a 2.5-fold shift to the left of the dose-response curve of the agonist, indicating an additive antinociceptive effect of **152** (table 6). By 24 hours, no significant effect could be observed when **152** (10 or 32 mg/kg) was administered sc. This initial antinociceptive action of **152** could

be antagonised by the selective μ-antagonist methocinnamox (M-CAM) as shown on figure 13 but not by norBNI **(13)** (data not shown), which suggests **152** is a μ-agonist when administered sc. In contrast, **13** (32 mg/kg) administered icv 24 hrs before U69593 (sc) produced a 4.1-fold shift to the right of the dose-response curve of the agonist, reflecting an expected antagonist effect of the drug.

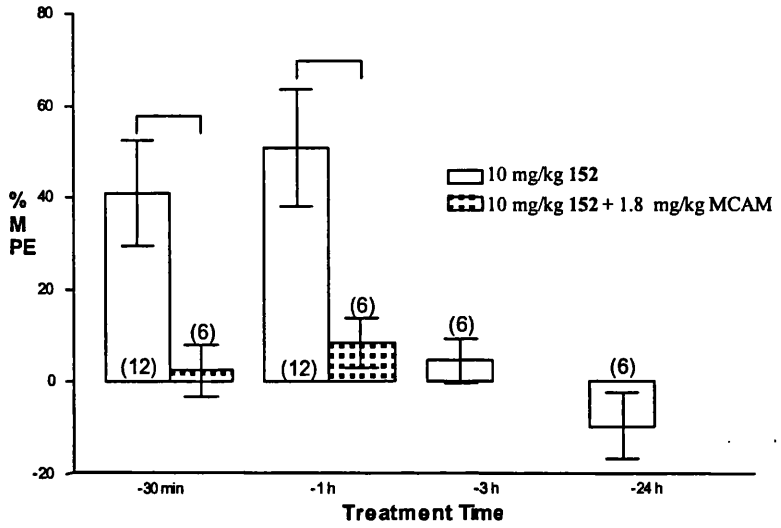



**Figure 13** Evaluation of agonist activity of **152** in the tail withdrawal assay

When BnorBNI **(152)** (10 nmol) was administered icv before administration sc of U69593, no antinociceptive effect was observed at any time (table 7) but instead **152** strongly antagonised the effect of U69593 with pretreatment times up to 168h (at this time, the shift was still 7-fold). After 1h pretreatment, administration (icv) of **152** (10 nmol) did not antagonise the effects of SNC80 and morphine (see table 7), which indicates **152** is a κ-antagonist when administered centrally. It is unclear why **152** did not exhibit any agonist activity when administered icv but it is noteworthy that similar contradicting observations were reported for 14-cinnamoylaminocodeinone, which displays potent μ-agonism with high efficacy when administered sc, but is a μ-antagonist devoid of any agonist effects when administered icv.[182,183]

Finally, we investigated whether the introduction of a benzyl group at the pyrrolic site of norBNI **(13)** was sufficient to produce an irreversible antagonist. An irreversible antagonist reduces the number of available receptors, rendering the number of receptors insufficient for an agonist to produce maximum response;

therefore, an irreversible antagonist will flatten and shift to the right the dose-response curve of an agonist. As shown on figure 14, both 10 nmol and 32 nmol administrations icv of **152**, 24 h before U69593 administration (sc), produced a flattening of the dose-response curve of the agonist, indicating a non-competitive interaction of **152** with κ-opioid receptors.

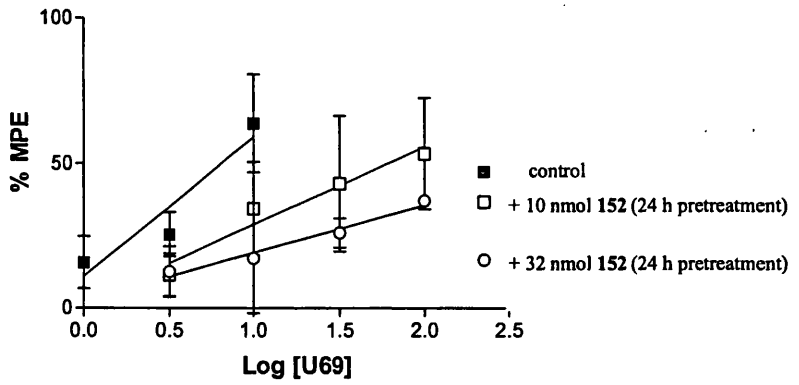



**Figure 14** Effect of **152** administration (icv) on the dose-response curve of U69593

The effect of equimolar administration (10 nmol, icv) of BnorBNI **(152)** and norBNI **(13)** was then compared (see figure 15); the pretreatment time was set at 24 h, since it represents the optimum time for **13** to be selective.

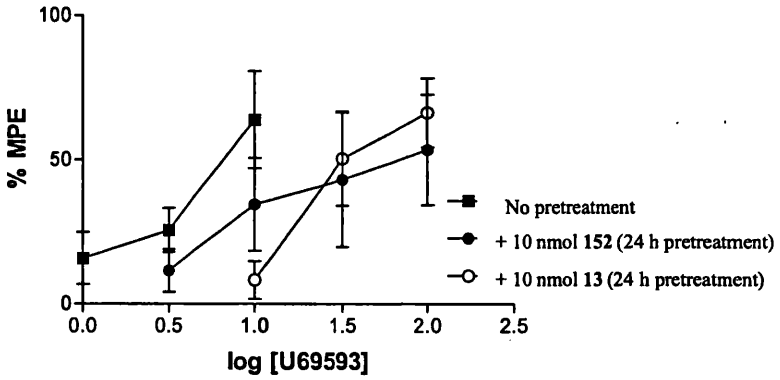



**Figure 15** Comparison of the effect of **13** and **152** (administered icv) on the dose-response curve of U69593 (administered sc)

Both compounds produced a rightward shift of the dose-response curve of U69593, with evidence of flattening of the U69593 dose-response curve observed upon administration of BnorBNI **(152)** but not of norBNI **(13)**; however, irreversible

antagonism upon administration of **13** was observed when higher doses of **13** (32 nmol, icv) were used (not shown on figure 15, but this is reflected by the fact that the U69593 dose-response curve was shifted beyond the agonist dose range, see table 7).

In conclusion, benzylation of the pyrrolic nitrogen of norBNI **(13)** has resulted in dramatic modification of the *in-vivo* pharmacological profile of the ligand; while **13** is a competitive κ-antagonist devoid of agonist effects when administered sc or icv, **152** is a partial μ-agonist with short duration of action when administered sc and an irreversible κ-antagonist upon central administration. Moreover, *in-vitro* pharmacological evaluation of **235** and **233** has revealed that replacement of the CPM groups (at 17- and 17'-N) of **13** and **152** with methyl groups has resulted in lower μ-agonist potency/increased μ-agonist efficacy than that displayed by the parent ligands with concomitant huge decrease in κ-antagonist potency.

### 3.3 Guanidinyl substituted ligands (50) and (51)

*p*-HydroxybenzylGNTI **(50)** and *m*-hydroxybenzylGNTI **(51)** were evaluated in opioid binding assays and in the *in-vitro* stimulation of [$^{35}$S]GTPγS binding assay; the results are reported in table 8 and table 9 respectively.

| | $K_i$ (nM) [a,b] | | | Selectivity | |
|---|---|---|---|---|---|
| | μ | δ | κ | κ/μ | κ/δ |
| **50** | 14.67 ± 3.65 | 41.86 ± 0.93 | 3.26 ± 0.12 | 4.5 | 13 |
| **51** | 14.16 ± 4.11 | 17.58 ± 0.29 | 2.74 ± 0.74 | 5 | 6 |
| **46** | 29.78 ± 0.50 | 82.05 ± 5.06 | 0.66 ± 0.05 | 45 | 129 |
| **11** | 36.9 ± 2.3 | 70.0 ± 0.3 | 0.18 ± 0.10 | 205 | 389 |
| **13** [c] | 21.0 ± 5.0 | 5.7 ± 0.9 | 0.20 ± 0.05 | 105 | 28 |

[a] Values are from 2 separate experiments, each performed in triplicate
[b] Radiolabeled ligands are [$^3$H]-DAMGO (for μ), [$^3$H]Cl-DPDPE (for δ) and [$^3$H]-U69593 (for κ).
[c] Data are from reference 180

**Table 8** Binding affinities to cloned human opioid receptors transfected into Chinese hamster ovary (CHO) cells

In the binding assay, both **50** and **51** displayed modest affinity for the κ-receptor with poor κ/μ selectivity (less than 5-fold for both compounds) and κ/δ selectivity (13-fold for **50** and 6-fold for **51**). In particular, the binding assay showed our efforts to recover κ-selectivity unsuccessful since both **50** and **51** exhibited lower κ-selectivity than that displayed by the pioneering ligand *p*-chlorobenzylGNTI **(46)** (45-fold κ/μ and 129-fold κ/δ selectivity). In comparison, norBNI **(13)** and GNTI **(11)**, the two standard κ-antagonists, displayed much higher κ-selectivity than **50** and **51** in this assay (up to 60 times higher).

In the functional assay, both **50** and **51** failed to stimulate [$^{35}$S]GTPγS binding for any type of opioid receptor (data not shown) and displayed potent and selective κ-antagonist effects (table 9).

| | $K_i$ (nM) [a,b] | | | Selectivity | |
|---|---|---|---|---|---|
| | μ | δ | κ | κ/μ | κ/δ |
| **50** | 12.66 ± 0.84 | 18.31 ± 0.95 | 0.10 ± 0.01 | 127 | 183 |
| **51** | 4.28 ± 0.52 | 4.35 ± 0.22 | 0.13 ± 0.02 | 33 | 33 |
| **46** | 5.24 ± 1.13 | 7.67 ± 1.36 | 0.14 ± 0.01 | 37 | 55 |
| **11** | 3.23 | 15.49 | 0.04 | 81 | 389 |
| **13** [c] | 18.9 ± 1.8 | 4.42 ± 0.38 | 0.04 ± 0.01 | 484 | 113 |

[a] Values are from 5 or 6 experiments
[b] Radiolabeled ligands are [$^3$H]-DAMGO (for μ), [$^3$H]Cl-DPDPE (for δ) and [$^3$H]-U69593 (for κ)
[c] Data are from reference 180

**Table 9** Antagonist potency in [$^{35}$S]GTPγS assays performed in cloned human opioid receptors

Interestingly, **50** exhibited a higher κ/μ selectivity than that observed with GNTI **(11)** (127- and 81-fold respectively) and higher κ/δ selectivity than that displayed by norBNI **(13)** (183- and 113-fold respectively). The κ-selectivity of **50** was about 4 or 5 times higher than that of the *p*-chlorobenzylGNTI analogue **(46)**, which shows that substitution with a hydroxy group in *p*-position has successfully led to recovery of selectivity towards the κ-receptor. In contrast, **51** showed less substantial selectivity (33-fold κ/μ and κ/δ selectivity) and its κ-selectivity was

broadly similar to that observed with **46**; these results thus appear to support the molecular modelling studies, which showed the superposition of the phenolic group of norBNI **(13)** and **50** to be much closer than that of norBNI **(13)** and **51**. It is also noteworthy that the improved κ-selectivity observed with **50** did not result from enhanced κ-potency but was rather a consequence of decreased potency at μ and δ-receptors due to the presence of the hydroxy group in *p*-position. Interestingly, this is in agreement with Thomas's earlier findings, who proposed that the oxygen atom of the second phenolic group of norBNI **(13)** might unfavourably interact with a group present in the lipophilic pocket of μ and δ-receptors.[104]

Finally, **46**, **50** and **51** failed to flatten the dose-response curve of the agonist U69593 (data not shown), which suggests they do not bind irreversibly towards the κ-receptor. It is interesting to note that, at the start of the present project, *p*-chlorobenzylGNTI **(46)** was believed to bind irreversibly towards the κ-receptor since its antagonist effects remained after washing the membranes (see figure 16). However, the irreversible character of **46** was not confirmed in further antagonist assays (data not shown), which suggests that wash-resistant binding does not represent a suitable criterion for assessment of irreversibility.

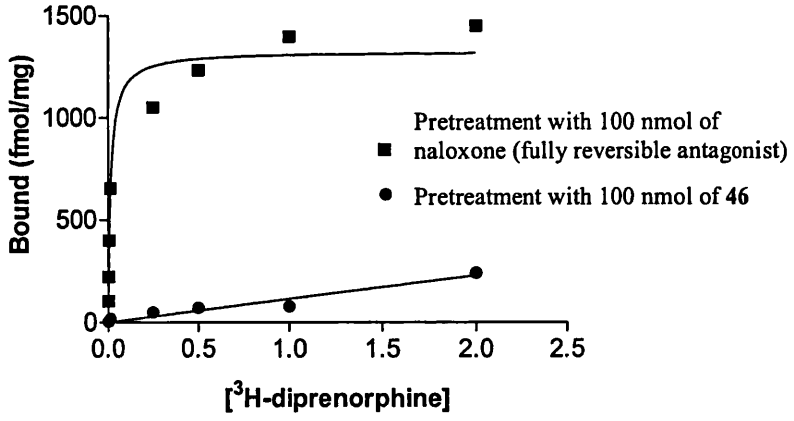



**Figure 16** Binding of [$^3$H]diprenorphine in κ-membranes (CHO cells) that have been pretreated with naloxone or **46** and extensively washed

# 4. EXPERIMENTAL

**Analytical specifications**

All chemicals were purchased from Aldrich, Acros or Lancaster chemical companies. All solvents were GPR grade, purchased from Merck or Fisher Scientific.

Column chromatography was performed under gravity over silica gel 60 (35-70μm) purchased from Merck, except for compounds **136**, **161**, **163**, **164** and **165**, which were purified on a pre-packed column of silica gel 60 (10g, 30-90μm, purchased from International Sorbent Technology) using "Flash master personal" equipment ("anti-gravity" elution). Analytical TLC was performed using aluminium-backed plates coated with Kieselgel 60 $F_{254}$, purchased from Merck. The chromatograms were visualised using either UV light (UVGL-58, short wavelength), ninhydrin (acidic) or PMA.

Infrared spectroscopy was performed on a Perkin-Elmer RX 1 FT-IR Instrument. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded using either JEOL GX 270 (operating at 270 MHz for $^{1}H$ and 67.8 MHz for $^{13}C$) or JEOL EX 400 (operating at 400 MHz for $^{1}H$ and 100.5 MHz for $^{13}C$) spectrometers. Chemical shifts are expressed in ppm. Spectra were referenced internally using either tetramethylsilane as the standard or using the residual solvent resonance. Coupling constants (*J*) are reported in Hz and the multiplicities abbreviated as follows: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). In the particular cases of morphinan-derived compounds, only diagnostic peaks have been recorded for proton NMR. High and low resolution fast atom bombardment (FAB) mass spectra were carried out on a Fisons VG AutoSpec Q instrument, with a matrix of *m*-nitrobenzylalcohol. High and low resolution electron impact (EI) mass spectra were recorded using EI ionisation at 70eV, on a VG AutoSpec instrument, equipped with a Fisons autosampler. All mass spectra were recorded in positive mode. Melting points were evaluated using a Gallenkamp MFB-595 melting point apparatus or a Reichert-Jung hot stage microscope apparatus and are uncorrected.

Microanalyses were performed with a Perkin-Elmer 240C analyser and were recorded by the Microanalysis Laboratory in the Department of Chemistry, University of Bath.

**General Procedure A – Guanidinylation of amine 53.**

A solution of **53** (1 equi.), mercury(II) chloride (1.5 equi.) and freshly distilled triethylamine (2 equi.) in anhydrous *N,N*-dimethylformamide (DMF) (15 mL) was cooled to 0°C under a nitrogen atmosphere. A solution of the guanidinylating agent (2 equi.) in anhydrous DMF (5 mL) was added and the mixture allowed to warm to room temperature. Stirring was continued at 60°C for 24 h, after which the reaction mixture was filtered through a short column of celite, eluting with acetate. Sodium bicarbonate (30 mL) was then added, the organic phase isolated and the aqueous phase further extracted with ethyl acetate. The organic phases were combined, washed with water and brine, dried over magnesium sulfate ($MgSO_4$) and concentrated. Purification by silica gel column chromatography, eluting first with dichloromethane (DCM) until removal of unreacted guanidinylating agent, then with DCM/MeOH/$NH_4OH$: 250/10/1, afforded the desired product.

**General procedure B – Preparation of guanidinylating agents. *N*-substitution of 54.**

A solution of 1,3-bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea **(54)** (1 equi.), sodium hydride (3 equi.) and crown ether (18-crown-6 or 15-crown-5, 0.1 equi.) in dry tetrahydrofuran (THF) or DMF (5 mL) was cooled to 0°C under a nitrogen atmosphere. Stirring was continued for 20 minutes at that temperature before adding the appropriate benzyl bromide derivative (2 equi.). The reaction mixture was then allowed to warm to room temperature and stirring continued for 22-41 hours at 70°C. The reaction was quenched by slow addition of water (5 mL), the organic phase isolated and the aqueous phase further extracted with diethyl ether. The combined organic phases were washed with brine and dried ($MgSO_4$). The crude product was purified by column chromatography, eluting first with *n*-hexanes/ethyl acetate: 20/1 then with *n*-hexanes/ethyl acetate: 9/1.

**General Procedure C – Mono-BOC-protection of diamines.**

To a solution of the diamine (1 equi.) in chloroform ($CHCl_3$) (100 mL) at 0°C was added dropwise a solution of di-*tert*-butyl-dicarbonate (0.1 equi.) in $CHCl_3$ (45 mL). The ice bath was removed and stirring continued at room temperature for 24 hours. Brine (25 mL) was added, the organic phase isolated and the aqueous phase further

extracted with diethyl ether. The organic phases were combined, dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography, eluting with DCM/MeOH/$NH_4OH$: 85/10/5, afforded the protected diamine.

**General Procedure D – Preparation of isothiocyanates from primary amines.**

To a solution of the primary amine (1 equi.) in $CHCl_3$ (50 mL) was added a solution of calcium carbonate (1 equi.) in water (4 mL). The mixture was stirred for 5 minutes at room temperature before adding thiophosgene (2 equi.) and stirring continued for a further 24 hours. The organic phase was isolated, washed with water, dried ($MgSO_4$) and concentrated. Purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 3/1, afforded the desired isothiocyanate.

**General Procedure E – Preparation of N,N'-disubstituted thioureas from isothiocyanates.**

To a solution of the isothiocyanate (1 equi.) in acetone (30 mL) was added dropwise $NH_4OH$ (concentrated aqueous solution, 10 equi.). The solution was stirred at room temperature for 24 hours, after which the solvents were removed under vacuum. Purification by silica gel column chromatography, eluting first with *n*-hexanes/ethyl acetate: 3/1 then with *n*-hexanes/ethyl acetate: 1/1, afforded the desired product.

**General Procedure F – BOC-Protection of N,N'-disubstituted thioureas.**

A solution of the disubstituted thiourea (1 equi.) and sodium hydride (2 equi.) in dry THF (90 mL) was stirred for 10 min at 0°C under a nitrogen atmosphere. A solution of di-*tert*-butyl-dicarbonate (2 equi.) in THF (20 mL) was then added, the ice bath removed and stirring continued overnight at room temperature. The reaction was quenched by addition of NaOH (aqueous solution, 0.1 M) and the mixture stirred for a further 20 min. The organic layer was isolated and the aqueous phase extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, afforded a mixture of mono and di-BOC-protected *N,N'*-disubstituted thioureas.

**General procedure G – TBDMS-Protection of benzyl alcohols.**

To a solution of imidazole (2 equi.) and *tert*-butyldimethylsilyl chloride (1.5 equi.) in dry THF (20 mL) under a nitrogen atmosphere was added slowly a solution of the alcohol (1 equi.) in dry THF (10 mL). The reaction mixture was stirred overnight at room temperature, then water was added (5mL) and the reaction mixture extracted three times with diethylether. The organic phase was dried ($MgSO_4$) and the solvent evaporated. The crude oil was then taken up in *n*-hexanes and filtration of the solid – washing with *n*-hexanes– afforded the protected alcohol. If no precipitation was observed, the crude oil was purified by column chromatography, eluting with *n*-hexanes/ethyl acetate: 10/1.

**General procedure H – Phthalimido-protection of primary amines.**

A solution of the primary amine (1 equi.) and phthalic anhydride (1 equi.) in mixed xylenes was refluxed overnight under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature and water was added. The aqueous phase was extracted several times with $CHCl_3$, the organic phase was dried ($MgSO_4$) and the solvent evaporated. Purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 6/1, afforded the desired phthalimide.

**General procedure I – N-Benzylation or N-alkykation of pyrrolic or indolic nitrogen.**

To a solution of **13** (or other pyrrole or indole derivative) (1 equi.) in dry THF or DMF (5 mL) under a nitrogen atmosphere were added sodium hydride (60% in oil, 4 equi.) and 18-crown-6 (0.1 equi.). This mixture was stirred for 20 minutes at room temperature before adding a solution of the appropriate benzyl bromide (3 equi.) in dry THF or DMF (2 mL) and stirring continued overnight at 70°C. The reaction was quenched with water (5 mL), the aqueous phase extracted several times with DCM/MeOH: 5/1, the organic phase dried ($MgSO_4$) and the solvent evaporated. The crude oil was purified by column chromatography, eluting with $CHCl_3$ until complete removal of unreacted benzyl bromide derivative, then with gradient elution ($CHCl_3$/MeOH/$NH_4OH$: 900/10/1 to $CHCl_3$/MeOH/$NH_4OH$: 200/10/1), which afforded the desired product.

**General procedure J – Preparation of α,α'-phthalimidobromoxylenes.**

A mixture of dibromoxylene (1 equi.), potassium phthalimide (1 equi.) and 18-crown-6 (0.1 equi.) in toluene (30 mL) was refluxed overnight under a nitrogen atmosphere. Water was then added, the organic phase isolated, dried ($MgSO_4$) and evaporated. Purification by flash chromatography, eluting with *n*-hexanes/ethyl acetate: 4/1, afforded the desired product.

**General procedure K – Preparation of pyrroles from morphinan-6-ones.**

A solution of morphinan-6-one (1 equi.) in anhydrous DMF (0.1 M) was heated to 100°C under a nitrogen atmosphere. A solution of hydrazine sulfate (ground into a thin powder, 0.53 equi.) in DMF was added to the solution. The mixture was stirred for 6 hours at 100°C, then cooled to room temperature and the solvent evaporated under vacuum. The residue was dissolved in dry dimethylsulfoxide (DMSO) (0.25 M) and a solution of methanesulfonic acid (0.50 equi.) in dry DMSO (0.6 M) was added. The mixture was stirred at 130°C under a nitrogen atmosphere for 3.5 hours. The solution was then cooled to room temperature, diluted with water (10 mL) and basified to pH = 10 with $NH_4OH$. The solution was extracted with DCM/MeOH:5/1, the organic phase was washed with brine and dried ($MgSO_4$). The solvent was removed by evaporation, yielding a dark brown oil that was purified by column chromatography (gradient elution, 100% DCM then DCM/MeOH/$NH_4OH$: 400/10/1 to DCM/MeOH/$NH_4OH$: 110/10/1).

**General procedure L – Conversion of benzyl alcohols into benzyl bromides.**

Bromine (1.2 equi.) was added dropwise to a solution of triphenylphosphine (1.2 equi.) and imidazole (1.2 equi.) in dry DCM (20 mL) under a nitrogen atmosphere and stirring continued at room temperature for a further 20 minutes. A solution of the benzyl alcohol (1 equi.) in dry DCM (5mL) was added dropwise and the reaction mixture stirred at room temperature until completion. The solvent was then evaporated and the crude product purified by column chromatography eluting with *n*-hexanes/ethyl acetate: 3/1.

**General procedure M – Reduction of benzaldehydes.**

A solution of the benzaldehyde (2 equi.) in dry THF (10 mL) was added dropwise to a suspension of sodium borohydride (1 equi.) in dry THF (10 mL) and the reaction mixture was stirred overnight at room temperature. Water (4 mL) and a diluted solution of acetic acid (2.5 mL) were then added, the organic phase isolated and the aqueous phase further extracted with diethyl ether (2x25 mL). The organic phases were combined, washed first with a solution of sodium hydrogencarbonate (2x10 mL) then with water (2x10 mL) and dried ($MgSO_4$). The solvent was evaporated and the product used without any further purification.

**General procedure N – Preparation of isothiocyanates from primary amines in the morphinan series.**

To a solution of the amine (1 equi.) in $CHCl_3$ (2 mL) was added a solution of sodium hydrogencarbonate (6 equi.) in water (0.7 mL). The mixture was stirred for 20 minutes before adding freshly distilled thiophosgene (1.1 equi.) and stirring continued for a further 2 hours. The organic phase was isolated and the aqueous phase extracted with $CHCl_3$. The organic phase was then dried ($MgSO_4$) and concentrated under vacuum. Purification of the crude product was performed on silica gel (10 g) using "Flash master personal" equipment and eluting under pressure and against gravity, first with 100% $CHCl_3$ then with gradient elution ($CHCl_3$/MeOH: 300/5 to $CHCl_3$/MeOH: 300/8).

**General procedure O – Deprotection of phthalimides.**

The protected amine (1 equi.) was dissolved in ethanol (1 mL) and the solution was warmed up when necessary till complete dissolution of the material. Hydrazine hydrate (3 to 5 equi.) was added and the reaction mixture was stirred till complete deprotection (16 to 48 hours). The solvent was then removed under vacuum and the crude product purified by column chromatography, eluting first with $CHCl_3$/MeOH/$NH_4OH$: 500/10/1, then with $CHCl_3$/MeOH/$NH_4OH$: 250/10/1.

**General procedure P – Deprotection of BOC groups with trifluoroacetic acid.**

The mixture of mono- and di-BOC-protected morphinans was dissolved in DCM (3 mL) and the solution was cooled to 0°C. Trifluoroacetic acid (2 mL) was added and

the solution stirred for a further 30 minutes at 0°C. The ice bath was then removed and stirring continued overnight at room temperature. After evaporation under vacuum, the oil was precipitated with diethyl ether and the solid washed several times with diethyl ether.

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino) [7,7'-bimorphinan]-3,3',14,14'-tetrol (norbinaltorphimine) (13)** [82]

Naltrexone hydrochloride (1.00 g, 2.65 mmol), hydrazine sulfate (0.18 g, 1.41 mmol) and methanesulfonic acid (0.08 mL, 1.31 mmol) were reacted according to the general procedure K. **13** was isolated as a brown solid (0.54 g, 62 %).

IR $\nu_{max}$/cm (KBr): 3382 (br, bonded OH), 3075 and 3001 (C-H aromatic); $^1$H NMR (400 MHz, $CDCl_3$): 0.12 (m, 4H, 2xNCH$_2$CH(C*H*HC*H*H)), 0.52 (m, 4H, 2xNCH$_2$CH(CH*H*CH*H*)), 0.79-0.88 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 5.69 (s, 2H, 5-H + 5'-H), 6.49 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.66 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 4.27 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 4.54 (2xNCH$_2$CH(CH$_2$*C*H$_2$)), 9.87 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 23.50 (10-C + 10'-C), 29.27 (8-C + 8'-C), 31.77 (15-C + 15'-C), 44.08 (16-C + 16'-C), 50.60 (13-C + 13'-C), 59.70 (18-C + 18'-C), 62.56 (9-C + 9'-C), 73.34 (14-C + 14'-C), 85.80 (5-C + 5'-C), 116.20 (7-C + 7'-C), 117.76 (2-C + 2'-C), 119.10 (1-C + 1'-C), 124.98 (C), 125.27 (C), 130.80 (12-C + 12'-C), 139.32 (3-C + 3'-C), 143.08 (4-C + 4'-C); MS (FAB): *m/z* = 662 (M+H); $C_{40}H_{43}N_3O_6$ requires 661; mp > 240°C

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-4-hydroxybenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (50)**

**68** (mixture of mono- and di-BOC protected derivatives) (90 mg, 0.10 mmol) was dissolved in a mixture of conc. HCl/MeOH (2.5 mL/2.5 mL) and the solution stirred overnight at room temperature. The solvents were then removed under vacuum, the solid washed several times with diethyl ether and dried under vacuum for several days. **50** (HCl salt) (0.058 g, 97%) was isolated as a brown solid.

IR $\nu_{max}$/cm (KBr): 3363-3234 (br, bonded OH and bonded NH), 1637 (C=N, NH and NH$_2$); $^1$H NMR (400 MHz, $CD_3OD$): 0.48-0.62 (m, 2H, NCH$_2$CH(C*H*HC*H*H)), 0.72-

0.93 (m, 2H, $NCH_2CH(CH\textit{H}CH\textit{H})$), 1.12-1.22 (m, 1H, $NCH_2C\textit{H}(CH_2CH_2)$), 4.26 (s, 2H, $CH_2$), 5.72 (s, 1H, 5-H), 6.64 (d, 1H, *J*=8.0 Hz, 1-H), 6.68 (d, 1H, *J*=8.0 Hz, 2-H), 6.94-7.03 (m, 2H, Ar), 7.22-7.50 (m, 5H, Ar); $^{13}C$ NMR (100.5 MHz, $CD_3OD$): 2.59 ($NCH_2CH(\textit{C}H_2CH_2)$), 5.50 ($NCH_2CH(CH_2\textit{C}H_2)$), 6.05 ($NCH_2\textit{C}H(CH_2CH_2)$), 24.22 (10-C), 28.75 ($CH_2$), 29.32 ($CH_2$), 46.60 ($CH_2$), 46.97 ($CH_2$), 48.88 (13-C), 57.88 (18-C), 62.49 (9-C), 72.58 (14-C), 83.78 (5-C), 108.98 (Ar), 112.69 (Ar), 113.55 (Ar), 115.08 (Ar), 116.96 (Ar), 118.17 (Ar), 119.59 (Ar), 120.99 (Ar), 121.53 (Ar), 125.62 (Ar), 127.28 (Ar), 129.08 (Ar), 129.58 (Ar), 131.29 (Ar), 136.92 (Ar), 140.82 (Ar), 143.51 (Ar), 155.44 (Ar), 157.40 (NCNN); MS (FAB): *m/z* = 578.2743 (M+H); $C_{34}H_{36}O_4N_5$ requires 578.2767; Anal. ($C_{34}H_{35}O_4N_5$:3HCl:$2H_2O$) requires C 56.47 %, H 5.85 %, N 9.68 %, found : C 56.20 %, H 6.01 %, N 9.28 %; mp > 250°C

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-3-hydroxybenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (51)**

**69** (mixture of mono- and di-BOC protected derivatives) (78 mg, 0.09 mmol) was dissolved in a mixture of conc. HCl/MeOH (2.5 mL/2.5 mL). A similar workup as used for the synthesis of **50** afforded **51** (HCl salt) as a brown solid (51 mg, 98%).

IR $\nu_{max}$/cm (KBr): 3348-3231 (br, bonded OH and bonded NH), 1637 (C=N, NH and $NH_2$); $^1H$ NMR (400 MHz, $CD_3OD$): 0.46-0.62 (m, 2H, $NCH_2CH(C\textit{H}HC\textit{H}H)$), 0.69-0.95 (m, 2H, $NCH_2CH(CH\textit{H}CH\textit{H})$), 1.08-1.21 (m, 1H, $NCH_2C\textit{H}(CH_2CH_2)$), 4.42 (s, 2H, $CH_2$), 5.70 (s, 1H, 5-H), 6.61-6.84 (m, 5H, Ar), 6.96 (d, 1H, *J*=8.4 Hz, Ar), 7.18 (t, 1H, *J*=8.4 Hz, Ar), 7.28-7.34 (m, 1H, Ar), 7.38-7.52 (m, 1H, Ar); $^{13}C$ NMR (67.8 MHz, $CD_3OD$): 4.25 ($NCH_2CH(\textit{C}H_2CH_2)$), 7.11 ($NCH_2CH(CH_2\textit{C}H_2)$), 7.69 ($NCH_2\textit{C}H(CH_2CH_2)$), 25.89 (10-C), 30.44 ($CH_2$), 31.01 ($CH_2$), 46.72 ($CH_2$), 48.29 ($CH_2$), 48.73 (13-C), 59.08 (18-C), 64.29 (9-C), 74.40 (14-C), 85.60 (5-C), 110.91 (Ar), 114.67 (Ar), 115.81 (Ar), 116.61 (Ar), 118.96 (Ar), 120.05 (Ar), 120.12 (Ar), 121.54 (Ar), 123.04 (Ar), 123.50 (Ar), 127.55 (Ar), 129.24 (Ar), 131.03 (Ar), 131.70 (Ar), 133.22 (Ar), 138.86 (Ar), 139.96 (Ar), 142.77 (Ar), 145.49 (Ar), 158.38 (Ar), 159.74 (NCNN); MS (FAB): *m/z* = 578.2748 (M+H); $C_{34}H_{36}O_4N_5$ requires 578.2767; Anal. ($C_{34}H_{35}O_4N_5$:3HCl:$2H_2O$) requires C 56.47 %, H 5.85 %, N 9.68 %, found : C 56.80 %, H 5.96 %, N 10.10 %; mp > 250°C

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N'*-4-methoxybenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (52)**

**73** (0.67 g, 1.62 mmol), **53** (0.35 g, 0.81 mmol), mercury(II) chloride (0.24 g, 1.34 mmol) and triethylamine (0.23 mL, 1.62 mmol) in DMF (18 mL) were reacted according to the general procedure A. A mixture containing the desired product **74** and the mono-BOC protected analogue was obtained as a brown solid (0.31 g, 48 %).

No NMR data available as the product collected was a mixture containing **74** and its mono-BOC protected derivative. MS (FAB): *m/z* = 692 (M+H, one BOC), 792 (M+H, two BOC); mono-BOC protected product: $C_{40}H_{45}N_5O_6$ requires 691; di-BOC protected product: $C_{45}H_{53}N_5O_8$ requires 791

A solution of the above mixture (0.15 g, 0.19 mmol) in DCM (3 mL) was treated with trifluoroacetic acid (2 mL) as described in the general procedure P and **52** (TFA salt) was isolated as a brown solid (0.17 g, 96%).

IR $\nu_{max}$/cm (KBr): 3200 (br, bonded OH and NH), 1678, 1643 (C=N, NH and $NH_2$); $^1$H NMR (270 MHz, $CD_3OD$): 0.43 (d, 2H, *J*=4.9 Hz, $NCH_2CH(CHHCHH)$), 0.63-0.80 (m, 2H, $NCH_2CH(CHHCHH)$), 1.01-1.09 (m, 1H, $NCH_2CH(CH_2CH_2)$), 3.67 (s, 3H, $CH_3$), 4.28 (s, 2H, $CH_2$), 5.61 (s, 1H, 5-H), 6.53-6.61 (m, 2H, 1-H and 2-H), 6.79-6.90 (m, 3H, Ar), 7.14-7.21 (m, 3H, Ar), 7.31-7.34 (m, 1H, Ar); $^{13}$C NMR (67.8 MHz, $CD_3OD$): 3.34 ($NCH_2CH(CH_2CH_2)$), 6.17 ($NCH_2CH(CH_2CH_2)$), 6.73 ($NCH_2CH(CH_2CH_2)$), 24.95 (10-C), 29.59 ($CH_2$), 30.11 ($CH_2$), 45.55 ($CH_2$), 47.46 ($CH_2$), 55.72 ($CH_3$), 58.87 (18-C), 63.56 (9-C), 73.51 (14-C), 84.78 (5-C), 110.00 (C), 113.80 (CH), 115.19 (CH), 118.08 (CH), 119.33 (CH), 120.60 (CH), 122.25 (CH), 122.48 (C), 126.83 (C), 128.42 (C), 129.46 (C), 129.68 (CH), 130.15 (C), 132.40 (C), 138.08 (C), 142.01 (C), 144.70 (C), 157.47 (C), 160.80 (CN); MS (FAB): *m/z* = 592.2895 (M+H), $C_{35}H_{38}N_5O_4$ requires 592.2923; Anal. ($C_{35}H_{37}N_5O_4$:3TFA) requires C 52.73 %, H 4.32 %, N 7.50 %, found : C 52.50 %, H 4.79 %, N 7.96; mp > 220°

**5'-Amino-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo [2',3':6,7]-morphinan (53)** [106]

Method A

To a solution of **56** (1.08 g, 2.38 mmol) in methanol (15 mL) were added 2 spatula of Raney nickel. The mixture was stirred at room temperature under a nitrogen atmosphere for 10 minutes, after which hydrazine hydrate (2.3 mL, 47.3 mmol) was slowly added and stirring continued at 55°C for a further 6 hours. The mixture was then filtered through a short column of celite, concentrated and purified by column chromatography, eluting with DCM/MeOH/$NH_4OH$: 110/10/1. **53** was isolated as a brown solid (0.47 g, 47 %).

Method B

A solution of **56** (2.50 g, 5.5 mmol) and iron(II)sulfate heptahydrate (13.62 g, 49.0 mmol) in methanol (120 mL), water (24 mL) and $NH_4OH$ (84 mL) was stirred at 80°C for 3 hours. The reaction mixture was then allowed to cool to room temperature, filtered and extracted, first with DCM then with DCM/MeOH: 5/1. The organic phase was dried ($MgSO_4$), concentrated under vacuum and the crude oil purified by column chromatography, eluting first with $CHCl_3$ then with $CHCl_3$/MeOH/$NH_4OH$: 250/10/1. **39** was isolated as a brown solid (1.31 g, 56 %).

$^1H$ NMR (270 MHz, $CD_3OD$): 0.32-0.38 (m, 2H, $NCH_2CH(CHHCHH)$), 0.65-0.76 (m, 2H, $NCH_2CH(CHHCHH)$), 0.91-1.02 (m, 1H, $NCH_2CH(CH_2CH_2)$), 5.74 (s, 1H, 5-H), 6.54 (d, 1H, *J*=8.3 Hz, 1-H), 6.70 (d, 1H, *J*=8.3 Hz, 2-H), 7.29 (m, 1H, 7'-H), 7.98 (m, 1H, 6'-H), 8.37 (m, 1H, 4'-H); $^{13}C$ NMR (67.8 MHz, $CD_3OD$): 3.42 ($NCH_2CH(CH_2CH_2)$), 3.89 ($NCH_2CH(CH_2CH_2)$), 8.63 ($NCH_2CH(CH_2CH_2)$), 23.31 (10-C), 28.26 ($CH_2$), 30.64 ($CH_2$), 43.81 (16-C), 47.28 (13-C), 58.47 (18-C), 62.17 (9-C), 72.48 (14-C), 84.65 (5-C), 104.02 (Ar), 109.23 (Ar), 111.83 (Ar), 113.67 (Ar), 117.01 (Ar), 118.41 (Ar), 124.08 (Ar), 126.48 (Ar), 129.13 (Ar), 130.35 (Ar), 132.61 (Ar), 137.05 (Ar), 139.42 (Ar), 143.10 (Ar); MS (FAB): *m/z* = 430 (M); $C_{26}H_{28}N_3O_3$ requires 430; $R_f$ (DCM/MeOH/$NH_4OH$: 110/10/1): 0.33

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-nitro-3,14-dihydroxyindolo [2',3':6,7]-morphinan (56)** [106]

A solution of naltrexone (3.00 g, 8.8 mmol) and 4-nitrophenylhydrazine (1.61 g, 10.5 mmol) in ethanol/conc. HCl (45 mL/45 mL) was refluxed for 24 h under a nitrogen atmosphere. The solvents were then removed under vacuum and the residue basified to pH = 10 with $NH_4OH$. The solution was extracted with DCM, the organic phase was dried ($MgSO_4$) and the solvent removed by evaporation. The dark residue was purified by column chromatography, eluting first with 100 % DCM, then with DCM/MeOH/$NH_4OH$: 300/10/1. **56** was isolated as a brown solid (1.07 g, 26 %).

IR $\nu_{max}$/cm (KBr): 3391 (br, bonded OH and bonded NH), 1156 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 0.10-0.26 (m, 2H, $NCH_2CH(CHHCHH)$), 0.48-0.61 (m, 2H, $NCH_2CH(CHHCHH)$), 0.86-1.03 (m, 1H, $NCH_2CH(CH_2CH_2)$), 5.50 (s, 1H, 5-H), 6.45-6.52 (m, 2H, 1-H and 2-H), 7.10-7.18 (m, 1H, Ar), 7.20-7.29 (m, 2H, Ar); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 4.08 ($NCH_2CH(CH_2CH_2)$), 4.14 ($NCH_2CH(CH_2CH_2)$), 9.28 ($NCH_2CH(CH_2CH_2)$), 23.24 (10-C), 27.94 ($CH_2$), 31.28 ($CH_2$), 43.51 (16-C), 48.12 (13-C), 59.23 (18-C), 62.08 (9-C), 72.49 (14-C), 84.36 (5-C), 110.08 (Ar), 113.59 (Ar), 114.97 (Ar), 116.87 (Ar), 117.83 (Ar), 119.97 (Ar), 124.72 (Ar), 125.86 (Ar), 130.28 (Ar), 131.87 (Ar), 138.24 (Ar), 139.36 (Ar), 139.84 (Ar), 143.02 (Ar); MS (FAB): *m/z* = 460 (M); $C_{26}H_{26}N_3O_5$ requires 460; $R_f$ (DCM/MeOH/$NH_4OH$: 89/10/1): 0.54; mp > 230°C (lit.: >230°C) [183a]

**4-(Benzyloxy)benzyl bromide (60)** [184,185]

Triphenylphosphine (1.57 g, 6.0 mmol), imidazole (0.408 g, 6.0 mmol), bromine (0.31 mL, 6.0 mmol) and **66** (1.07 g, 5.0 mmol) in dry DCM (25mL) were reacted according to general procedure L. **60** was obtained as a white solid after purification by column chromatography (1.29 g, 93%).

IR $\nu_{max}$/cm (neat): 3064 and 3030 (C-H aromatic); $^1$H NMR (400 MHz, $CDCl_3$): 4.50 (s, 2H, $CH_2Br$), 5.06 (s, 2H, $CH_2$), 6.92-6.96 (m, 2H, Ar), 7.25-7.44 (m, 7H, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 34.01 ($CH_2Br$), 70.02 ($CH_2O$), 114.97 (CH), 127.31 (CH), 127.91 (CH), 128.48 (CH), 130.03 (C), 130.31 (CH), 136.49 (C), 158.61 (C); $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.93; mp : 82°C (lit.: 78-82°C) [184]

**3-(Benzyloxy)benzyl bromide (61)** [184,186]

Triphenylphosphine (3.51 g, 13.4 mmol), imidazole (0.91 g, 13.4 mmol), bromine (0.69 mL, 13.4 mmol) and **67** (2.39 g, 11.2 mmol) in dry DCM (15mL) were reacted according to general procedure L. **61** was obtained as a colourless solid after purification by column chromatography (2.73 g, 88%).

IR $\nu_{max}$/cm (neat): 3063 and 3032 (C-H aromatic); $^1$H NMR (400 MHz, $CDCl_3$): 4.47 (s, 2H, $CH_2Br$), 5.07 (s, 2H, $CH_2$), 6.90-6.93 (m, 1H, Ar), 6.99-7.03 (m, 2H, Ar), 7.24-7.46 (m, 6H, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 33.56 ($CH_2Br$), 69.99 ($CH_2O$), 114.82 (CH), 115.29 (CH), 121.42 (CH), 127.38 (CH), 127.90 (CH), 128.46 (CH), 129.70 (CH), 136.52 (C), 138.99 (C), 158.71 (C); MS (FAB): *m/z* = 276 (M, $^{79}$Br), 277 (M+H, $^{79}$Br), 278 (M, $^{81}$Br), 279 (M+H, $^{81}$Br); $C_{14}H_{13}OBr$ requires 277; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.93; mp : 37°C (lit.: 37-39°C)[186]

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-benzyloxybenzyl)-2-methyl-2-thiopseudourea (62)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (0.79 g, 2.7 mmol), sodium hydride (60% in oil, 0.13 g, 3.3 mmol) and **60** (0.83 g, 3.0 mmol) in dry DMF (11 mL) were reacted according to the procedure B. Purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/2, afforded **62** as a very viscous colourless oil (0.91 g, 62 %).

IR $\nu_{max}$/cm (neat): 2978, 2932 (C-H aromatic), 1742 (carbamate), 1715 (C=N), 1612 (carbamate), 1153 (C-N); $^1$H NMR (270MHz, $CDCl_3$): 1.42 (s, 9H, $C(CH_3)_3$), 1.53 (s, 9H, $C(CH_3)_3$), 2.27 (s, 3H, $SCH_3$), 4.72 (s, 2H, $CH_2N$), 5.05 (s, 2H, $CH_2O$), 6.91-6.96 (d, 2H, *J*=8.4 Hz, Ar), 7.25-7.43 (m, 7H, Ar); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 15.53 ($SCH_3$), 27.95 (2x$C(CH_3)$), 51.79 ($CH_2N$), 69.92 ($CH_2O$), 81.71 ($C(CH_3)$), 82.56 ($C(CH_3)$), 114.63 (CH), 127.44 (CH), 127.89 (CH), 128.50 (CH), 129.31 (CH), 129.65 (C), 136.89 (C), 152.17 (C), 157.99 (CO), 158.15 (CO), 163.40 (CN); MS (FAB): *m/z* = 487 (M+H); $C_{26}H_{34}N_2O_5S$ requires 486; $R_f$ (*n*-hexanes/ethyl acetate: 9/2): 0.47

**1,3-Bis-*tert*-butoxycarbonyl-1-(3'-benzyloxybenzyl)-2-methyl-2-thiopseudourea (63)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (0.29 g, 1.01 mmol), sodium hydride (60% in oil, 48 mg, 1.21 mmol) and **61** (0.31 g, 1.11 mmol) in dry DMF (5 mL) were reacted according to the procedure B. After purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/2, **63** was isolated as a very viscous colourless oil (0.29 g, 54 %).

IR $\nu_{max}$/cm (neat): 2978, 2931 (C-H aromatic), 1721 (br, C=N), 1611 (carbamate), 1140 (C-N); $^1$H NMR (400 MHz, $CDCl_3$): 1.39 (s, 9H, $C(CH_3)_3$), 1.52 (s, 9H, $C(CH_3)_3$), 2.28 (s, 3H, $SCH_3$), 4.76 (s, 2H, $CH_2N$), 5.06 (s, 2H, $CH_2O$), 6.94 (m, 2H, Ar), 7.01 (s, 1H, 2-H), 7.21-7.26 (m, 2H, Ar), 7.29-7.44 (m, 5H, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 15.72 ($SCH_3$), 28.04 ($C(CH_3)$), 28.13 ($C(CH_3)$), 52.40 ($CH_2N$), 69.84 ($CH_2O$), 81.65 ($C(CH_3)$), 82.71 ($C(CH_3)$), 113.63 (CH), 114.08 (CH), 120.05 (CH), 127.32 (CH), 127.74 (CH), 128.38 (CH), 129.25 (CH), 136.82 (C), 138.83 (C), 151.66 (3-C), 157.71 (CO), 158.63 (CO), 163.08 (CN); $R_f$ (*n*-hexanes/ethyl acetate: 9/2): 0.52

**4-(Benzyloxy)benzaldehyde (64)** [187,188]

To a solution of 4-hydroxybenzaldehyde (1.22 g, 10.0 mmol) and anhydrous potassium carbonate (2.07 g, 15.0 mmol) in dry DMF (5mL) was added dropwise a solution of benzyl bromide (1.71 g, 1.2 mL, 10.0 mmol) in dry DMF (1mL). The mixture was stirred overnight at room temperature under a nitrogen atmosphere. Water (3 mL) was then added and the solution extracted with diethyl ether (2x25 mL). The organic phase was washed with water (2x10 mL), dried ($MgSO_4$) and the solvent removed by evaporation. **64** was isolated as a white solid and used without any further purification (1.94 g, 91 %).

IR $\nu_{max}$/cm (KBr): 3034 and 3071 (C-H aromatic), 2810 and 2727 (C-H aldehyde), 1694 (CO); $^1$H NMR (400 MHz, $CDCl_3$): 5.15 (s, 2H, $CH_2$), 7.07 (d, 2H, $J$=8.6 Hz), 7.32-7.45 (m, 5H, Ph), 7.83 (d, 2H, $J$=8.6 Hz), 9.89 (s, 1H, CHO); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 70.25 ($CH_2O$), 115.01 (CH), 127.34 (CH), 128.19 (CH), 128.58 (CH), 129.93 (C), 131.84 (CH), 135.74 (C), 163.47 (C), 190.51 (CO); MS (FAB): $m/z$ = 213

(M+H); $C_{14}H_{12}O_2$ requires 212; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.87; mp. : 65 °C (lit.: 67-68°C)[188]

**3-(Benzyloxy)benzaldehyde (65)** [188,189]

3-Hydroxybenzaldehyde (1.22 g, 10.0 mmol), anhydrous potassium carbonate (2.07 g, 15.0 mmol) and benzyl bromide (1.71 g, 1.2 mL, 10.0 mmol) in dry DMF were reacted as for the synthesis of **64**. **65** was isolated as a white solid and used without any further purification (2.02 g, 95 %).

IR $\nu_{max}$/cm (KBr): 3024 and 3055 (C-H aromatic), 2829 and 2744 (C-H aldehyde), 1686 (CO); $^1$H NMR (400 MHz, $CDCl_3$): 5.13 (s, 2H, $CH_2$), 7.26 (m, 1H), 7.33-7.49 (m, 8H), 9.97 (s, 1H, CHO); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 70.19 ($CH_2O$), 113.07 (CH), 122.06 (CH), 123.56 (CH), 127.39 (CH), 128.06 (CH), 128.52 (CH), 129.96 (CH), 136.10 (C), 137.61 (C), 159.05 (C), 191.79 (CO); MS (FAB): *m/z* = 213 (M+H); $C_{14}H_{12}O_2$ requires 212; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.87; mp : 52°C (lit.: 52-53°C)[190]

**4-(Benzyloxy)benzyl alcohol (66)** [185,187]

Sodium borohydride (0.38 g, 5.0 mmol) and **64** (2.12 g, 10.0 mmol) in dry THF (20 mL) were reacted according to the general procedure M. **66** was isolated as a white solid (2.0 g, 93 %).

IR $\nu_{max}$/cm (KBr): 3329 (br, bonded OH), 3060 and 3034 (C-H aromatic); $^1$H NMR (270 MHz, $CDCl_3$): 4.49 (s, 2H, $CH_2$OH), 5.05 (s, 2H, $CH_2$), 6.93 (d, 2H, *J*=8.4 Hz, Ar), 7.25-7.45 (m, 7H, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 64.74 ($CH_2$OH), 69.89 ($CH_2O$), 114.66 (CH), 127.23 (CH), 127.74 (CH), 128.36 (CH), 128.41 (CH), 133.16 (C), 136.67 (C), 157.98 (C); MS (FAB): *m/z* = 214 (M), 215 (M+H); $C_{14}H_{14}O_2$ requires 214; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.64; mp : 83°C (lit.: 86-90°C)[191]

**3-(Benzyloxy)benzyl alcohol (67)** [191]

**65** (1.06 g, 5.0 mmol) and sodium borohydride (0.19 g, 5.0 mmol) in dry THF (10 mL) were reacted according to the general procedure M. This afforded **67** as a white solid (0.90 g, 84 %).

IR $\nu_{max}$/cm (KBr): 3340 (br, bonded OH), 3063 and 3032 (C-H aromatic); $^1$H NMR (400 MHz, $CDCl_3$): 4.64 (s, 2H, C*H*$_2$OH), 5.07 (s, 2H, $CH_2$), 6.90-7.03 (m, 3H, Ar), 7.25-7.46 (m, 6H, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 65.15 ($CH_2OH$), 69.89 ($CH_2O$), 113.06 (CH), 113.94 (CH), 119.21 (CH), 126.81 (CH), 127.32 (CH), 127.47 (CH), 127.80 (CH), 128.41 (CH), 129.45 (CH), 136.73 (C), 142.37 (C), 158.77 (C); MS (FAB): *m/z* = 214 (M), 215 (M+H); $C_{14}H_{14}O_2$ requires 214; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.72; mp : 44°C (lit.: 44.5-45°C)[190]

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-4-benzyloxybenzyl)guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (68)**

**62** (0.35, 0.72 mmol), **53** (0.153 g, 0.36 mmol), mercury(II) chloride (0.158 g, 0.58 mmol) and triethylamine (0.10 mL, 0.72 mmol) in dry DMF (10 mL) were reacted according to the general procedure A. A mixture containing **68** and the mono-BOC protected analogue was obtained as a brown solid (0.11 g, 35%).

Data for di-BOC protected product:

IR $\nu_{max}$/cm (KBr): 3368 (br, bonded OH and bonded NH), 1671 (C=N); $^1$H NMR (400 MHz, $CDCl_3$): 0.09-0.17 (m, 2H, $NCH_2CH(CHHCHH)$), 0.45-0.58 (m, 2H, $NCH_2CH(CHHCHH)$), 0.80-0.92 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.38 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 4.85 (s, 2H, $CH_2$), 5.03 (s, 2H, $CH_2O$), 5.60 (s, 1H, 5-H), 6.45 (d, 1H, *J*=7.8 Hz, 1-H), 6.56 (d, 1H, *J*=7.8 Hz, 2-H), 6.64-7.06 (m, 4H, Ar), 7.29-7.43 (m, 8H, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 4.25 ($NCH_2CH(CH_2CH_2)$), 4.42 ($NCH_2CH(CH_2CH_2)$), 9.92 ($NCH_2CH(CH_2CH_2)$), 23.62 (10-C), 28.04 ($C(CH_3)$), 28.60 ($C(CH_3)$), 29.26 ($CH_2$), 31.90 ($CH_2$), 43.81 (16-C), 48.34 ($CH_2N$), 50.84 (13-C), 59.85 (18-C), 62.75 (9-C), 70.29 ($CH_2O$), 72.75 (14-C), 80.14 ($C(CH_3)$), 82.02 ($C(CH_3)$), 85.29 (5-C), 111.94 (Ar), 112.54 (Ar), 114.64 (Ar), 115.03 (Ar), 117.51 (Ar), 118.57 (Ar), 119.07 (Ar), 124.93 (Ar), 126.97 (Ar), 127.53 (Ar), 127.63(Ar), 128.15 (Ar), 128.73 (Ar), 129.94 (Ar), 130.51 (Ar), 130.89 (Ar), 130.97 (Ar), 135.47 (Ar), 137.09 (Ar), 139.65 (Ar), 143.11 (Ar), 152.64 (Ar), 158.10 (CO), 158.35 (CO), 162.82 (NCNN); MS (FAB): *m/z* = 868 (M+H); $C_{51}H_{57}N_5O_8$ requires 867; $R_f$ (DCM/MeOH/$NH_4OH$: 110/10/1): 0.57

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-3-benzyloxybenzyl)guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (69)**

**63** (0.52 g, 1.07 mmol), **53** (0.23 g, 0.53 mmol), mercury(II) chloride (0.158 g, 0.88 mmol) and triethylamine (0.15 mL, 1.07 mmol) in dry DMF (12 mL) were reacted according to the general procedure A. A mixture containing **69** and the mono-BOC protected analogue was obtained as a brown solid (0.14 g, 30%).

Data for di-BOC protected product:

IR $\nu_{max}$/cm (KBr): 3362 (br, bonded OH and bonded NH), 1671 (C=N); $^1$H NMR (400 MHz, $CDCl_3$): 0.12-0.20 (m, 2H, $NCH_2CH(CHHCHH)$), 0.51-0.62 (m, 2H, $NCH_2CH(CHHCHH)$), 0.99-1.12 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.37 (s, 9H, $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$), 4.98 (s, 2H, $CH_2N$), 5.02 (s, 2H, $CH_2O$), 5.61 (s, 1H, 5-H), 6.49 (d, 1H, *J*=8.2 Hz, 1-H), 6.58 (d, 1H, *J*=8.2 Hz, 2-H), 6.67-7.38 (m, 12H, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 3.92 ($NCH_2CH(CH_2CH_2)$), 4.11 ($NCH_2CH(CH_2CH_2)$), 9.53 ($NCH_2CH(CH_2CH_2)$), 23.18 (10-C), 28.03 ($C(CH_3)$), 28.15 ($C(CH_3)$), 28.70 ($CH_2$), 31.37 ($CH_2$), 43.46 (16-C), 47.96 ($CH_2N$), 50.60 (13-C), 59.43 (18-C), 62.41 (9-C), 69.74 ($CH_2O$), 72.36 (14-C), 81.95 ($C(CH_3)$), 82.55 ($C(CH_3)$), 84.97 (5-C), 111.51 (Ar), 112.32 (Ar), 114.27 (Ar), 114.75 (Ar), 117.16 (Ar), 118.11 (Ar), 118.76 (Ar), 121.56 (Ar), 124.62 (Ar), 126.60 (Ar), 127.25 (Ar), 127.42 (Ar), 127.61 (Ar), 128.25 (Ar), 129.21 (Ar), 129.98 (Ar), 130.48 (Ar), 135.00 (Ar), 136.72 (Ar), 136.93 (Ar), 139.12 (Ar), 142.63 (Ar), 143.72 (Ar), 149.32 (Ar), 158.35 (CO), 158.44 (CO), 162.46 (NCNN); MS (FAB): *m/z* = 868.4294 (M+H); $C_{51}H_{58}N_5O_8$ requires 868.4285; $R_f$ (DCM/MeOH/$NH_4OH$: 110/10/1): 0.57

**4-Methoxybenzaldehyde (70)** [192]

To a mixture of 4-hydroxybenzaldehyde (6.10 g, 50.0 mmol) and anhydrous potassium carbonate (10.35 g, 75.0 mmol) in dry DMF (25mL) was added dropwise methyl iodide (3.1 mL, 50.0 mmol). The mixture was stirred overnight at room temperature under a nitrogen atmosphere. Water (15 mL) was added and the solution extracted with diethyl ether (2x50 mL). The organic phase was washed with brine (2x20 mL), dried ($MgSO_4$) and concentrated under vacuum. **70** was used without any further purification and isolated as an orange oil (6.26 g, 92 %).

IR $\nu_{max}$/cm (neat): 2840 and 2740 (C-H aldehyde), 1682 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 3.85 (s, 3H, $CH_3$), 6.98 (d, 2H, *J*=8.8 Hz), 7.81 (d, 2H, *J*=8.8 Hz), 9.86 (s, 1H, CHO); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 55.86 ($CH_3$), 114.47 (CH), 130.02 (C), 132.06 (CH), 164.64 (C), 190.77 (CHO); MS (EI): *m/z* = 136.0510 (M), $C_8H_8O_2$ requires 136.0524; $R_f$ (*n*-hexanes/ethyl acetate: 6/1): 0.44

**4-Methoxybenzyl alcohol (71)** [193]

A suspension of sodium borohydride (1.52 g, 40.0 mmol) in dry THF (35 mL) and a solution of **70** (5.44 g, 40.0 mmol) in dry THF (35 mL) were reacted according to the general procedure M. **71** was obtained as a yellow oil (5.49 g, 99 %).

IR $\nu_{max}$/cm (neat): 3338 (br, bonded OH), 3064 and 3033 (C-H aromatic); $^1$H NMR (270 MHz, $CDCl_3$): 2.95 (br, s, 1H, OH), 3.76 (s, 3H, $CH_3$), 4.51 (s, 2H, C$H_2$OH), 6.84 (d, 2H, *J*=8.6 Hz), 7.23 (d, 2H, *J*=8.6 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 55.08 ($CH_3$), 64.40 ($CH_2$), 113.68 (CH), 128.44 (CH), 133.04 (C), 158.83 (C); MS (EI): *m/z* = 138.0682 (M), $C_8H_{10}O_2$ requires 138.0680; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.51

**4-Methoxybenzyl bromide (72)** [194,195]

Triphenylphosphine (6.25 g, 24.0 mmol), imidazole (1.63 g, 24.0 mmol), bromine (1.22 mL, 24.0 mmol) and **71** (2.76 g, 20.0 mmol) in dry DCM (100mL) were reacted according to the general procedure L. **72** was used with no further purification (only a small quantity of the crude product has been purified on column chromatography for NMR characterisation).

$^1$H NMR (270 MHz, $CDCl_3$): 3.78 (s, 3H, $CH_3$), 4.49 (s, 2H, C$H_2$Br), 6.85 (d, 2H, *J*=8.6 Hz), 7.31 (d, 2H, *J*=8.6 Hz); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 34.50 ($CH_2Br$), 55.70 ($CH_3$), 114.45 (CH), 130.14 (C), 130.67 (CH), 159.78 (C)

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-methoxybenzyl)-2-methyl-2-thiopseudourea (73)** [196]

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (5.35 g, 18.2 mmol), sodium hydride (60% in oil, 1.41 g, 35.2 mmol), 15-crown-5 (0.2 mL, 1.0 mmol) and 4-methoxybenzyl bromide **(72)** (4.02 g, 20.0 mmol) in dry DMF (27 ml) were reacted

according to the general procedure B. **73** was isolated as a very viscous colourless oil (4.0 g, 49 %).

IR $\nu_{max}$/cm (neat): 1719 (C=N), 1613 (carbamate), 1141 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.40 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 2.24 (s, 3H, $SCH_3$), 3.77 (s, 3H, $OCH_3$), 4.69 (s, 2H, $CH_2$), 6.83 (d, 2H, *J*=9.0 Hz), 7.26 (d, 2H, *J*=9.0 Hz); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 15.43 ($SCH_3$), 27.91 ($C(CH_3)$), 27.94 ($C(CH_3)$), 51.74 ($CH_2$), 55.04 ($OCH_3$), 81.49 ($C(CH_3)$), 82.39 ($C(CH_3)$), 113.63 (CH), 129.26 (CH), 151.87 (C), 157.87 (CO), 158.98 (CO), 163.05 (CN); MS (FAB): *m/z* = 411.1952 (M+H); $C_{20}H_{31}N_2O_5S$ requires 411.1953; $R_f$ (*n*-hexanes/ethyl acetate: 5/1): 0.33

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-3,4-dichlorobenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (75)**

**78** (0.49 g, 1.09 mmol), **53** (0.24 g, 0.55 mmol), mercury(II) chloride (0.22 g, 0.83 mmol) and triethylamine (0.15 mL, 1.10 mmol) in dry DMF (10 ml) were reacted according to the general procedure A. A mixture containing 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-3,4-dichlorobenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan **(82)** and the corresponding mono-BOC-protected analogue was obtained as a brown solid (0.34 g, 74 %).

No NMR data available. IR **(82)** $\nu_{max}$/cm (neat): 3393 (br, bonded OH), 1712 (C=N), 1611 (carbamate); MS (FAB): *m/z* = 730 (M+H, $^{35}Cl_2$), 732 (M+H, $^{35}Cl^{37}Cl$), 830 (M+H, $^{35}Cl_2$), 832 (M+H, $^{35}Cl^{37}Cl$); mono-BOC protected product: $C_{39}H_{41}{}^{35}Cl_2N_5O_5$ requires 730; di-BOC protected product: $C_{44}H_{49}{}^{35}Cl_2N_5O_7$ requires 830; HRMS (di-Boc protected compound): 830.3088 (M+H, $^{35}Cl_2$), 832.3080 (M+H, $^{35}Cl^{37}Cl$); $C_{44}H_{50}{}^{35}Cl_2N_5O_7$ requires 830.3087 and $C_{44}H_{50}{}^{35}Cl^{37}ClN_5O_7$ requires 832.3057; $R_f$ (DCM/MeOH/$NH_4OH$: 200/12/1): 0.66

The above mixture (0.26 g, 0.31 mmol) was dissolved in DCM (3 mL) and treated with trifluoroacetic acid (2 mL) as described in the general procedure P. **75** (TFA salt) was isolated as a brown solid (0.25 g, 90%).

IR $\nu_{max}$/cm (KBr): 3193 (br, bonded OH and NH), 1678 and 1633 (C=N, NH and $NH_2$); $^1$H NMR (270 MHz, $CD_3OD/CDCl_3$: 6/1): 0.52 (d, 2H, *J*=4.2 Hz,

$NCH_2CH(CHHCHH)$), 0.72-0.88 (m, 2H, $NCH_2CH(CHHCHH)$), 2.32 (s, 3H, $CH_3$), 4.45 (s, 2H, $CH_2$), 5.69 (s, 1H, 5-H), 6.64-6.71 (m, 2H, 1-H and 2-H), 6.97 (d, 1H, *J*=8.7 Hz, 6'-H), 7.22-7.27 (m, 2H), 7.41 (d, 1H, *J*=8.7 Hz, 4'-H), 7.47-7.50 (m, 2H); $^{13}C$ NMR (67.8 MHz, $CD_3OD/CDCl_3$: 6/1): 3.85 ($NCH_2CH(CH_2CH_2)$), 6.70 ($NCH_2CH(CH_2CH_2)$), 7.22 ($NCH_2CH(CH_2CH_2)$), 25.44 (10-C), 30.02 ($CH_2$), 30.57 ($CH_2$), 45.18 ($CH_2$), 47.85($CH_2$), 48.36 (13-C), 59.33 (18-C), 63.96 (9-C), 73.97 (14-C), 85.24 (5-C), 110.47 (C), 114.37 (CH), 118.49 (CH), 119.82 (CH), 121.15 (CH), 122.65 (CH), 122.92 (C), 127.15 (C), 128.36 (CH), 128.85 (C), 130.67 (CH), 132.27 (CH), 132.85 (C), 133.05 (C), 134.03 (C), 138.51 (C), 139.09 (C), 142.43 (C), 145.12 (C), 158.11 (NCNN); MS (FAB): *m/z* = 630.2026 (M+H, $^{35}Cl_2$), 632.2014 (M+H, $^{35}Cl^{37}Cl$), 634.2019 (M+H, $^{37}Cl_2$), $C_{34}H_{34}{}^{35}Cl_2N_5O_3$ requires 630.2038, $C_{34}H_{34}{}^{35}Cl^{37}ClN_5O_3$ requires 632.2008, $C_{34}H_{34}{}^{37}Cl_2N_5O_3$ requires 634.1979; Anal. ($C_{34}H_{33}N_5O_3Cl_2$:2TFA:$2H_2O$) requires C 51.01 %, H 4.39 %, N 7.83 %, found : C 50.90 %, H 4.03 %, N 7.78 %; mp: 190°C

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-4-methylbenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (76)**

**77** (0.43 g, 1.09 mmol), **53** (0.24 g, 0.55 mmol), mercury(II) chloride (0.22 g, 0.83 mmol) and triethylamine (0.15 mL, 1.10 mmol) in dry DMF (10 ml) were reacted according to the general procedure A. A mixture containing 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-4-methylbenzyl)guanidinyl -3,14-dihydroxyindolo [2',3':6,7]-morphinan **(81)** and the corresponding mono-BOC protected analogue was obtained as a brown solid (0.29 g, 68 %).

No NMR data available as the product collected contained a mixture of di-BOC protected compound **(81)** and its mono-BOC protected derivative; IR $\nu_{max}$/cm (neat): 3395 (br, bonded OH), 1706 (C=N), 1609 (carbamate); MS (FAB): *m/z* = 676 (M+H), 776 (M+H); mono-BOC protected product: $C_{40}H_{45}N_5O_5$ requires 675; di-BOC protected product: $C_{45}H_{53}N_5O_7$ requires 775; HRMS (FAB) *m/z* = 776.4037 (M+H), $C_{45}H_{54}N_5O_7$ requires 776.4023; $R_f$ (DCM/MeOH/$NH_4OH$: 200/12/1): 0.66

The above mixture (0.19 g, 0.24 mmol) in DCM (3 mL) was deprotected with trifluoroacetic acid (2 mL) as described in the general procedure P and **76** (TFA salt) was isolated as a brown solid (0.22 g, 96%).

IR $\nu_{max}$/cm (KBr): 3310 (br, bonded OH and NH), 1681 (C=N, NH and $NH_2$); $^1H$ NMR (270 MHz, $CD_3OD/CDCl_3$: 6/1): 0.53 (d, 2H, *J*=4.0 Hz, $NCH_2CH(CHHCHH)$), 0.74-0.93 (m, 2H, $NCH_2CH(CHHCHH)$), 2.32 (s, 3H, $CH_3$), 4.23 (d, 1H, *J*=6.0 Hz, C*H*H), 4.41 (s, 2H, $CH_2$), 5.72 (s, 1H, 5-H), 6.64 (d, 1H, *J*=8.2 Hz, 1-H), 6.68 (d, 1H, *J*=8.2 Hz, 2-H), 7.01 (dd, 1H, *J*=1.8Hz and *J*=8.7 Hz, 6'-H), 7.18 (d, 2H, *J*=8.9 Hz), 7.20 (d, 2H, *J*=8.9 Hz), 7.33 (d, 1H, *J*=1.8 Hz, 7'-H), 7.44 (d, 1H, *J*=8.7 Hz, 4'-H); $^{13}C$ NMR (67.8 MHz, $CD_3OD/CDCl_3$: 6/1): 3.86 ($NCH_2CH(CH_2CH_2)$), 6.69 ($NCH_2CH(CH_2CH_2)$), 7.16 ($NCH_2CH(CH_2CH_2)$), 21.72 ($CH_3$), 25.39 (10-C), 29.96 ($CH_2$), 30.52 ($CH_2$), 46.19 ($CH_2$), 47.87 ($CH_2$), 48.29 (13-C), 59.30 (18-C), 63.90 (9-C), 73.90 (14-C), 85.18 (5-C), 110.38 (C), 114.27 (CH), 118.52 (CH), 119.77 (CH), 121.04 (CH), 122.66 (CH), 122.74 (C), 127.09 (C), 128.61 (CH), 128.79 (C), 130.47 (C), 130.87 (CH), 132.78 (C), 134.79 (C), 138.45 (C), 139.19 (C), 142.39 (C), 145.06 (C), 157.90 (NCNN); MS (FAB): *m/z* = 575.2952 (M), 576.3008 (M+H); $C_{35}H_{38}N_5O_3$ requires 576.2974; Anal. ($C_{35}H_{37}N_5O_3$:3TFA:$2H_2O$) requires C 51.62 %, H 4.65 %, N 7.34 %, found : C 51.30 %, H 4.42 %, N 7.28 %; mp > 190°C (decomposition)

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-methylbenzyl)-2-methyl-2-thiopseudourea (77)**
1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (2.90 g, 10.0 mmol), sodium hydride (60% in oil, 0.44 g, 11.0 mmol), 15-crown-5 (0.2 mL, 1 mmol) and 4-methylbenzyl bromide (2.22 g, 12.0 mmol) in dry DMF (20 ml) were reacted according to the general procedure B. **77** was isolated as a colourless oil (2.93 g, 74 %).

IR $\nu_{max}$/cm (neat): 3350 (br, bonded OH), 1612 (carbamate); $^1H$ NMR (270 MHz, $CDCl_3$): 1.40 (s, 9H, $C(CH_3)_3$), 1.51 (s, 9H, $C(CH_3)_3$), 2.26 (s, 3H, $SCH_3$), 2.31 (s, 3H, $CH_3$), 4.72 (s, 2H, $CH_2$), 7.11 (d, 2H, *J*=7.9 Hz), 7.21 (d, 2H, *J*=7.9 Hz); $^{13}C$ NMR (67.8 MHz, $CDCl_3$): 14.79 ($SCH_3$), 20.43 ($CH_3$), 27.26 ($C(CH_3)$), 27.32 ($C(CH_3)$), 51.43 ($CH_2$), 80.76 ($C(CH_3)$), 81.73 ($C(CH_3)$), 127.08 (CH), 128.34 (CH), 133.58 (C),

136.27 (C), 151.21 (CO), 157.15 (CO), 162.35 (CN); MS (FAB): *m/z* = 395.2007 (M+H); $C_{20}H_{31}N_2O_4S$ requires 395.2004; $R_f$ (*n*-hexanes/ethyl acetate: 5/1): 0.42

**1,3-Bis-*tert*-butoxycarbonyl-1-(3',4'-dichlorobenzyl)-2-methyl-2-thiopseudourea (78)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (2.90 g, 10.0 mmol), sodium hydride (60% in oil, 0.44 g, 11.0 mmol), 15-crown-5 (0.2 mL, 1 mmol) and 3,4-dichlorobenzyl chloride (1.66 mL, 12.0 mmol) in dry DMF (20 ml) were reacted according to the general procedure B. **78** was isolated as a colourless oil (2.11 g, 47 %).

IR $\nu_{max}$/cm (neat): 1721 (C=N), 1617 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 1.41 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 2.31 (s, 3H, $SCH_3$), 4.68 (s, 2H, $CH_2$), 6.94 (m, 2H), 7.19 (dd, 1H, *J*=8.2 Hz and *J*=1.9Hz), 7.38 (d, 1H, *J*=8.2 Hz), 7.42 (d, 1H, *J*=1.9 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 15.17 ($SCH_3$), 27.50 ($C(CH_3)$), 27.54 ($C(CH_3)$), 50.72 ($CH_2$), 81.41 ($C(CH_3)$), 82.70 ($C(CH_3)$), 126.82 (CH), 129.43 (CH), 129.92 (CH), 130.99 (C), 131.86 (C), 137.21 (C), 151.28 (CO), 157.21 (CO), 161.82 (CN); MS (FAB): *m/z* = 449.1051 (M+H, $^{35}Cl_2$) and 451.1032 (M+H, $^{35}Cl^{37}Cl$); $C_{19}H_{27}{}^{35}Cl_2N_2O_4S$ requires 449.1067; $C_{19}H_{27}{}^{35}Cl^{37}ClN_2O_4S$ requires 451.1037; $R_f$ (*n*-hexanes/ethyl acetate: 5/1): 0.40

***N*-(*tert*-Butyloxycarbonyl)diaminoethane (83)** [197,198,199]

Diaminoethane (12.02 g, 200 mmol) in $CHCl_3$ (150 mL) and di-*tert*-butyl-dicarbonate (4.36 g, 20 mmol) in $CHCl_3$ (70 mL) were reacted according to the general procedure C. Purification by silica gel chromatography, eluting with DCM/MeOH/$NH_4OH$: 85/10/5, gave **83** (2.57 g, 80%) as a colourless oil.

IR $\nu_{max}$/cm (neat): 3360 (br, bonded NH), 1693 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 1.28 (s, br, 2H, $NH_2$), 1.33 (s, 9H, $C(CH_3)_3$), 2.64-2.73 (m, 2H, $CH_2NH_2$), 3.00-3.12 (m, 2H, $CH_2NH$), 5.42 (s, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 28.08 ($C(CH_3)_3$), 41.53 ($CH_2NH_2$), 43.09 ($CH_2NH$), 78.61 ($C(CH_3)_3$), 156.04 (CO); MS (FAB): *m/z* = 161 (M+H); $C_7H_{16}N_2O_2$ requires 160; $R_f$ (DCM/MeOH/$NH_4OH$: 85/10/5): 0.29

***N*-(*tert*-Butyloxycarbonyl)diaminobutane (84)** [200,201]

1,4-Diaminobutane (9.0 mL, 90 mmol) in $CHCl_3$ (90 mL) and di-*tert*-butyl-dicarbonate (1.95 g, 9 mmol) in $CHCl_3$ (45 mL) were reacted according to the general procedure C. Purification by silica gel column chromatography, eluting with DCM/MeOH/$NH_4OH$: 85/10/5, afforded the desired product **84** as a colourless oil (1.51 g, 89%).

IR $\nu_{max}$/cm (neat): 3358 (br, bonded NH), 1694 (carbamate); $^1H$ NMR (270 MHz, $CDCl_3$): 1.27 (s, br, 2H, $NH_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.46-1.56 (m, 4H, 2x$CH_2$), 2.69 (t, 2H, *J*=6.2 Hz, $CH_2NH_2$), 3.12 (t, 2H, *J*=6.2 Hz, $CH_2NH$), 4.95 (s, br, 1H, NH); $^{13}C$ NMR (67.8 MHz, $CDCl_3$): 27.85 ($CH_2$), 28.80 ($C(CH_3)_3$), 31.27 ($CH_2$), 40.75 ($CH_2NH_2$), 42.17 ($CH_2NH$), 79.17 ($C(CH_3)_3$), 156.13 (CO); MS (FAB): *m/z* = 189 (M+H), 377 (2M+H); $C_9H_{20}N_2O_2$ requires 188; $R_f$ (DCM/MeOH/$NH_4OH$: 85/10/5): 0.33

***N*-(*tert*-Butyloxycarbonyl)diaminohexane (85)** [197]

1,6-Diaminohexane (10.47 g, 90 mmol) in $CHCl_3$ (90 mL) and di-*tert*-butyl-dicarbonate (1.95 g, 9 mmol) in $CHCl_3$ (45 mL) were reacted according to the general procedure C. Purification by silica gel column chromatography, eluting with DCM/MeOH/$NH_4OH$: 85/10/5, afforded **85** as a colourless oil (1.73 g, 89%).

IR $\nu_{max}$/cm (neat): 3357 (br, bonded NH), 1692 (carbamate); $^1H$ NMR (270 MHz, $CDCl_3$): 1.28 (s, br, 2H, $NH_2$), 1.31-1.37 (m, 4H, 2x$CH_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.48-1.54 (m, 4H, 2x$CH_2$), 2.68 (t, 2H, *J*=6.6 Hz, $CH_2NH_2$), 3.08-3.13 (m, 2H, $CH_2NH$), 4.77 (s, br, 1H, NH); $^{13}C$ NMR (67.8 MHz, $CDCl_3$): 26.93 ($CH_2$), 27.02 ($CH_2$), 28.81 ($C(CH_3)_3$), 30.42 ($CH_2$), 34.07 ($CH_2$), 40.83 ($CH_2$), 42.45 ($CH_2$), 79.16 ($C(CH_3)_3$), 156.11 (CO); MS (FAB): *m/z* = 217 (M+H); $C_{11}H_{24}N_2O_2$ requires 216; $R_f$ (DCM/MeOH/$NH_4OH$: 85/10/5): 0.40

**[[(1,1-Dimethylethoxy)carbonyl]amino]ethylisothiocyanate (86)** [199]

**83** (2.50 g, 15.6 mmol), calcium carbonate (1.53 g, 15.6 mmol) and thiophosgene (2.40 mL, 31.2 mmol) in $CHCl_3$ (50 mL) were reacted according to the general procedure D. Purification by column chromatography yielded **86** as a white solid (2.60 g, 82%).

IR $\nu_{max}$/cm (neat): 3348 (br, bonded NH), 2978 (br, N-H), 2198 and 2113 (isothiocyanate), 1694 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 1.46 (s, 9H, $C(CH_3)_3$), 3.38 (virtual quartet, 2H, *J*=5.5 Hz, $CH_2NH$), 3.65 (t, 2H, *J*=5.5 Hz, $CH_2NCS$), 5.02 (s, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 28.41 ($C(CH_3)_3$), 40.63 ($CH_2$), 43.97 ($CH_2$), 80.02 ($C(CH_3)_3$), 132.23 (NCS), 155.55 (CO); MS (FAB): *m/z* = 203 (M+H) and 405 (2M+H); $C_8H_{14}N_2O_2S$ requires 202; $R_f$ (*n*-hexanes/ethyl acetate:4/1): 0.33; mp : 62°C (lit. : 63-64°C)[199]

**[[(1,1-Dimethylethoxy)carbonyl]amino]butylisothiocyanate (87)**

**84** (1.73 g, 9.2 mmol), calcium carbonate (0.90 g, 9.2 mmol) and thiophosgene (1.41 mL, 18.4 mmol) in $CHCl_3$ (50 mL) were reacted according to the general procedure D. After purification by column chromatography, **87** was isolated as a yellowish oil (1.90 g, 90%).

IR $\nu_{max}$/cm (neat): 3357 (br, bonded NH), 2978 (br, N-H), 2185 and 2107 (isothiocyanate), 1698 (carbamate); $^1$H NMR (75.45 MHz, $CDCl_3$): 1.43 (s, 9H, $C(CH_3)_3$), 1.35-1.55 (m, 2H, $CH_2$), 1.67-1.73 (m, 2H, $CH_2$), 3.09 (virtual quartet, 2H, *J*=6.3 Hz, $CH_2NH$), 3.53 (t, 2H, *J*=6.3 Hz, $CH_2NCS$), 4.84-4.91 (m, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 27.27 ($CH_2$), 27.38 ($CH_2$), 28.45 ($C(CH_3)_3$), 39.46 ($CH_2$), 44.63 ($CH_2$), 79.16 ($C(CH_3)_3$), 130.05 (NCS), 155.88 (CO); MS (FAB): *m/z* = 231 (M+H); $C_{10}H_{18}N_2O_2S$ requires 230; $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.33

**[[(1,1-Dimethylethoxy)carbonyl]amino]hexylisothiocyanate (88)**

**85** (1.75 g, 8.1 mmol), calcium carbonate (0.80 g, 8.1 mmol) and thiophosgene (1.22 mL, 16.2 mmol) in $CHCl_3$ (50 mL) were reacted according to the general procedure D. **88** was isolated as a colourless oil (1.61 g, 77%) after purification by column chromatography (elution with *n*-hexanes/ethyl acetate: 3/1).

IR $\nu_{max}$/cm (neat): 3351 (br, bonded NH), 2976 (br, N-H), 2183, 2105 (isothiocyanate), 1693 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 1.29 (s, 9H, $C(CH_3)_3$), 1.41-1.65 (m, 8H, 4x$CH_2$), 3.01 (virtual quartet, 2H, *J*=6.4 Hz, $CH_2NH$), 3.43 (t, 2H, *J*=6.4 Hz, $CH_2NCS$), 4.79-4.86 (m, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 28.47 ($CH_2$), 28.50 ($CH_2$), 29.65 ($C(CH_3)_3$), 40.80 ($CH_2$), 42.00 ($CH_2$), 42.13

($CH_2$), 46.02 ($CH_2$), 78.78 ($C(CH_3)_3$), 129.54 (NCS), 155.74 (CO); MS (FAB): *m/z* = 259 (M+H); $C_{12}H_{22}N_2O_2S$ requires 258; $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.34

**1,1-Dimethylethoxycarbonyl *N*-(2-(thioureido)ethyl)carbamate (89)**

A solution of **86** (2.54 g, 12.6 mmol) in acetone (30 mL) and $NH_4OH$ (14.43 mL, 0.25 mol) were reacted according to the general procedure E. After purification by column chromatography, **89** was isolated as a white solid (2.26 g, 82%).

IR $\nu_{max}$/cm (KBr): 3404-3190 (br, bonded NH), 2980 (br, N-H), 1686 (carbamate), 1243 (C=S), 1152 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.44 (s, 9H, $C(CH_3)_3$), 3.23-3.31 (m, 2H, $CH_2$), 3.44-3.48 (m, 2H, $CH_2$), 3.64 (s, br, 1H, NH), 5.57-5.90 (m, br, 2H, 2xNH), 6.43 (s, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 28.37 ($C(CH_3)_3$), 40.18 ($CH_2$), 45.27 ($CH_2$), 80.06 ($C(CH_3)_3$), 157.24 (CO), 184.09 (CS); MS (FAB): *m/z* = 220 (M+H); $C_8H_{17}N_3O_2S$ requires 219; $R_f$ (ethyl acetate: 100%): 0.57; mp : 127°C

**1,1-Dimethylethoxycarbonyl *N*-(4-(thioureido)butyl)carbamate (90)** [201]

A solution of **87** (2.50 g, 10.8 mmol) in acetone (30 mL) and $NH_4OH$ (12.46 mL, 0.22 mol) were reacted according to the general procedure E. After purification by column chromatography, **90** was isolated as a white solid (2.35 g, 88%).

IR $\nu_{max}$/cm (neat): 3305 (br, bonded NH), 2977, 2932 (br, N-H), 1682 (carbamate), 1252 (C=S), 1169 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.43 (s, 9H, $C(CH_3)_3$), 1.49-1.68 (m, 6H, 3x$CH_2$), 3.06-3.18 (m, 2H, $CH_2$), 3.53 (s, br, 1H, NH), 5.09 (s, br, 1H, NH), 6.52 (s, br, 1H, NH), 6.75 (s, br, 1H, NH); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 26.67 ($CH_2$), 27.97 ($CH_2$), 28.87 ($C(CH_3)_3$), 40.61 ($CH_2$), 45.21 ($CH_2$), 79.82 ($C(CH_3)_3$), 156.88 (CO), 183.21 (CS); MS (FAB): *m/z* = 248 (M+H); $C_{10}H_{21}N_3O_2S$ requires 247; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.26; mp : 152°C (lit. : 157-159°C)[201]

**1,1-Dimethylethoxycarbonyl *N*-(6-(thioureido)hexyl)carbamate (91)**

A solution of **88** (3.07 g, 11.9 mmol) in acetone (30 mL) and $NH_4OH$ (13.55 mL, 0.24 mol) were reacted according to the general procedure E. After purification by column chromatography, **91** was isolated as an off-white solid (3.21 g, 98%).

IR $\nu_{max}$/cm (neat): 3305 (br, bonded NH), 2977, 2933 (br, N-H), 1687 (carbamate), 1529 (N-H), 1252 (C=S), 1170 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.31-1.38 (m, 6H, 3x$CH_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.45-1.50 (m, 2H, $CH_2$), 1.56-1.63 (m, 2H, $CH_2$), 3.06-3.10 (m, 2H, $CH_2$), 3.52 (s, br, 1H, NH), 4.85 (s, br, 1H, NH), 6.36 (s, br, 2H, $NH_2$); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 26.45 ($CH_2$), 28.87 ($C(CH_3)_3$), 29.12 ($CH_2$), 30.23 ($CH_2$), 40.61 ($CH_2$), 45.28 ($CH_2$), 60.78 ($CH_2$), 79.69 ($C(CH_3)_3$), 156.67 (CO), 183.33 (CS); MS (FAB): *m/z* = 276 (M+H); $C_{10}H_{21}N_3O_2S$ requires 275; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.37; mp : 77°C

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-2-*tert*-butoxycarbonylamino-ethyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (95)**

A solution of the disubstituted thiourea **89** (2.13 g, 9.7 mmol), sodium hydride (0.776 g, 19.4 mmol) and di-*tert*-butyl-dicarbonate (2.33 g, 10.7 mmol) in dry THF (110 mL) were reacted according to the general procedure F. After purification, a mixture containing **92** and the mono-BOC protected analogue was isolated. $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.5

**53** (0.269 g, 0.63 mmol), mercury(II) chloride (0.255 g, 0.94 mmol), triethylamine (0.17 mL, 1.25 mmol) and **92** (mixture of mono and di-BOC-protected thioureas) (0.40 g, 1.25 mmol) were reacted according to the general procedure A. After purification, a mixture containing **95** and the mono-BOC protected analogue was isolated as a brown solid (0.09 g, 20%).

$^1$H NMR (270 MHz, $CDCl_3$, di-BOC protected derivative): 0.16 (d, 2H, *J*=4.8 Hz, $NCH_2CH(CHHCHH)$), 0.57 (d, 2H, *J*=8.1 Hz, $NCH_2CH(CHHCHH)$), 0.85-0.96 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.30 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 4.87 (s, br, 1H, NH), 5.25 (s, br, 1H, NH), 5.63 (s, 1H, 5-H), 6.50 (d, 1H, *J*=7.8 Hz, 1-H), 6.63 (d, 1H, *J*=7.8 Hz, 2-H), 6.82 (m, 1H, 6'-H), 7.12 (m, 1H, 7'-H), 7.21 (m, 1H, 4'-H), 8.89 (s, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CDCl_3$, mono-BOC protected derivative): 3.89 ($NCH_2CH(CH_2CH_2)$), 4.04 ($NCH_2CH(CH_2CH_2)$), 9.69 ($NCH_2CH(CH_2CH_2)$), 22.86 (10-C), 28.44 ($C(CH_3)_3$), 28.97 ($CH_2$), 31.62 ($CH_2$), 39.49 ($CH_2$), 42.56 ($CH_2$), 43.84 ($CH_2$), 48.24 (13-C), 59.76 (18-C), 62.68 (9-C), 72.90 (14-C), 79.80 ($C(CH_3)_3$), 85.52

(5-C), 110.87 (C), 111.70 (CH), 117.43 (CH), 117.63 (CH), 119.11 (CH), 125.25 (C), 127.18 (CH), 130.00 (C), 130.11 (C), 131.06 (C), 134.60 (C), 139.46 (C), 143.37 (C), 151.44 (C), 159.98 (CO), 162.49 (NCNN); $R_f$ (DCM/MeOH/$NH_4OH$: 200/10/1): 0.25

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-4-*tert*-butoxycarbonylamino-butyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (96)**

A solution of the disubstituted thiourea **90** (0.54 g, 2.18 mmol), sodium hydride (0.174 g, 4.36 mmol) and di-*tert*-butyl-dicarbonate (0.95 g, 4.36 mmol) in dry THF (25 mL) were reacted according to the general procedure F. After purification, a mixture containing **93** and the mono-BOC protected analogue was isolated (0.49 g, 65%). $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.5

**53** (0.278 g, 0.65 mmol), mercury(II) chloride (0.263 g, 0.97 mmol), triethylamine (0.18 mL, 1.30 mmol) and **93** (mixture of mono and di-BOC-protected thioureas) (0.45 g, 1.30 mmol) were reacted according to the general procedure A. After purification, a mixture containing **96** and the mono-BOC protected analogue was isolated as a brown solid (0.19 g, 39%).

Data for di-BOC protected product:

IR $\nu_{max}$/cm (neat): 3319 (br, bonded OH and NH), 2976 (br, N-H), 1697 (C=N, NH and $NH_2$), 1149 (C-N); $^1H$ NMR (400 MHz, $CDCl_3$): 0.13-0.18 (m, 2H, $NCH_2CH(CHHCHH)$), 0.52-0.61 (m, 2H, $NCH_2CH(CHHCHH)$), 0.83-0.95 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.10-1.22 (m, 2H, $CH_2$), 1.40 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 4.52 (s, br, 1H, NH), 4.93 (s, br, 1H, NH), 5.68 (s, 1H, 5-H), 6.49 (d, 1H, *J*=7.8 Hz, 1-H), 6.63 (d, 1H, *J*=7.8 Hz, 2-H), 6.70 (s, 1H, 6'-H), 7.09 (m, 1H, 7'-H), 7.17 (m, 1H, 4'-H), 9.83 (s, br, 1H, NH); $^{13}C$ NMR (100.5 MHz, $CDCl_3$): 4.33 ($NCH_2CH(CH_2CH_2)$), 4.53 ($NCH_2CH(CH_2CH_2)$), 9.89 ($NCH_2CH(CH_2CH_2)$), 23.54 ($CH_2$), 27.26 ($CH_2$), 28.53 ($CH_2$), 28.62 ($C(CH_3)_3$), 28.87 ($C(CH_3)_3$), 29.10 ($CH_2$), 31.90 ($CH_2$), 40.29 ($CH_2$), 40.77 ($CH_2$), 44.01 ($CH_2$), 48.31 (13-C), 59.81 (18-C), 62.60 (9-C), 73.10 (14-C), 78.75 ($C(CH_3)_3$), 79.40 ($C(CH_3)_3$), 85.18 (5-C), 111.15 (C), 113.06 (CH), 117.37 (CH), 117.58 (CH), 119.14 (CH), 121.52 (CH), 124.88 (C), 126.78 (C), 127.35 (C), 130.92 (C), 131.29 (C), 136.41 (C), 139.97 (C), 143.38 (C),

156.28 (CO), 159.91 (CO), 162.84 (NCNN); MS (FAB): *m/z* = 743 (M+H); $C_{41}H_{54}N_6O_7$ requires 742; $R_f$ (DCM/MeOH/$NH_4OH$: 200/10/1): 0.40

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N'*-6-*tert*-butoxycarbonylamino-hexyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (97)**

A solution of the disubstituted thiourea **91** (0.83 g, 3.01 mmol), sodium hydride (0.24 g, 6.02 mmol) and di-*tert*-butyl-dicarbonate (1.31 g, 6.02 mmol) in dry THF (45 mL) were reacted according to the general procedure F. After purification, a mixture containing **94** and the mono-BOC protected analogue was isolated (0.82 g, 72%). $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.45

**53** (0.24 g, 0.55 mmol), mercury(II) chloride (0.22 g, 0.82 mmol), triethylamine (0.15 mL, 1.1 mmol) and **94** (mixture of mono and di-BOC-protected thioureas) (0.41 g, 1.10 mmol) were reacted according to the general procedure A. After purification, a mixture containing **97** and the mono-BOC protected analogue was isolated as a brown solid (0.12 g, 28%).

Data for mono-BOC protected product:

IR $\nu_{max}$/cm (neat): 3389 (br, bonded OH and NH), 2976 (br, N-H), 1697 (C=N, NH and $NH_2$), 1149 (C-N); $^1H$ NMR (270 MHz, $CDCl_3$): 0.11-0.21 (m, 2H, $NCH_2CH(CHHCHH)$), 0.50-0.61 (m, 2H, $NCH_2CH(CHHCHH)$), 0.83-0.93 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.01-1.12 (m, 2H, $CH_2$), 1.18-1.30 (m, 2H, $CH_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.46-1.51 (m, 2H, $CH_2$), 4.67 (s, br, 1H, NH), 5.71 (s, 1H, 5-H), 6.52 (d, 1H, *J*=8.1 Hz, 1-H), 6.65 (d, 1H, *J*=8.1 Hz, 2-H), 6.81 (m, 1H, 6'-H), 7.12 (m, 1H, 7'-H), 7.26 (m, 1H, 4'-H), 9.30 (s, br, 1H, NH); $^{13}C$ NMR (67.8 MHz, $CDCl_3$): 3.72 ($NCH_2CH(CH_2CH_2)$), 3.98 ($NCH_2CH(CH_2CH_2)$), 9.33 ($NCH_2CH(CH_2CH_2)$), 23.05 ($CH_2$), 25.97 ($CH_2$), 26.15 ($CH_2$), 27.97 ($CH_2$), 28.41 ($C(CH_3)_3$), 29.25 ($CH_2$), 29.51 ($CH_2$), 31.49 ($CH_2$), 40.27 ($CH_2$), 40.77 ($CH_2$), 43.62 ($CH_2$), 47.85 (13-C), 59.40 (18-C), 62.18 (9-C), 72.74 (14-C), 78.38 ($C(CH_3)_3$), 85.06 (5-C), 110.74 (C), 113.38 (CH), 116.93 (CH), 117.57 (CH), 118.78 (CH), 121.13 (CH), 124.36 (C), 126.37 (C), 127.11 (C), 130.62 (C), 131.11 (C), 136.41 (C), 140.28 (C), 143.33 (C), 159.87 (CO), 164.05 (NCNN); MS (FAB): *m/z* = 671 (M+H); $C_{38}H_{50}N_6O_5$ requires 670; $R_f$ (DCM/MeOH/$NH_4OH$: 200/10/1): 0.41

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-2-aminoethyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (98)**

**95** (mixture of mono and di-BOC-protected products) (108 mg, 0.15 mmol) was dissolved in a mixture of conc. HCl/methanol (2.5 mL/2.5 mL). The solution was stirred overnight at room temperature then the solvent was removed until dryness. The solid was washed several times with diethyl ether then dried under vacuum, yielding **98** (HCl salt) as a brown solid (70 mg, 95%).

IR $\nu_{max}$/cm (KBr): 3400 (br, bonded OH and NH), 1623 (C=N, NH and $NH_2$); $^1$H NMR (270 MHz, $CD_3OD$): 0.46 (d, 2H, *J*=4.7 Hz, $NCH_2CH(CHHCHH)$), 0.69-0.79 (m, 2H, $NCH_2CH(CHHCHH)$), 1.01-1.12 (m, 1H, $NCH_2CH(CH_2CH_2)$), 5.64 (s, 1H, 5-H), 6.56 (d, 1H, *J*=8.1 Hz, 1-H), 6.60 (d, 1H, *J*=8.1 Hz, 2-H), 6.92-6.98 (m, 1H, 6'-H), 7.25-7.38 (m, 2H, 7'-H and 4'-H); $^{13}$C NMR (100.5 MHz, $CD_3OD$): 3.38 ($NCH_2CH(CH_2CH_2)$), 6.29 ($NCH_2CH(CH_2CH_2)$), 6.87 ($NCH_2CH(CH_2CH_2)$), 25.04 ($CH_2$), 29.69 ($CH_2$), 30.26 ($CH_2$), 39.59 ($CH_2N$), 40.23 ($CH_2N$), 47.57 (16-C), 48.02 (13-C), 58.86 (18-C), 63.52 (9-C), 73.62 (14-C), 84.85 (5-C), 110.17 (C), 113.85 (CH), 118.43 (CH), 119.31 (CH), 120.65 (CH), 122.33 (CH), 122.66 (C), 126.54 (C), 128.55 (C), 130.28 (C), 132.52 (C), 138.25 (C), 142.08 (C), 144.76 (C), 157.81 (NCNN); MS (FAB): *m/z* = 515 (M+H); $C_{29}H_{34}N_6O_3$ requires 514; Anal. ($C_{29}H_{34}N_6O_3$:4HCl:2$H_2O$) requires C 50.0 %, H : 6.0 %, N : 12.0 %, found C 50.6 %, H : 5.7 %, N : 11.5 %; mp > 225°C

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-4-aminobutyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (99)**

**96** (mixture of mono and di-BOC-protected products) (93 mg, 0.13 mmol) was dissolved in a mixture conc. HCl/methanol (2.5 mL/2.5 mL). The solution was stirred overnight at room temperature then the solvent was removed until dryness. The solid was washed several times with diethyl ether then dried under vacuum, yielding **99** (HCl salt) as a brown solid (64 mg, 99%).

IR $\nu_{max}$/cm (KBr): 3401 (br, bonded OH and NH), 1635 (C=N, NH and $NH_2$); $^1$H NMR (270 MHz, $CD_3OD$): 0.43-0.62 (m, 2H, $NCH_2CH(CHHCHH)$), 0.69-0.92 (m, 2H, $NCH_2CH(CHHCHH)$), 1.07-1.23 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.59-1.90 (m,

4H, 2x$CH_2$), 2.62-2.90 (m, 2H, $CH_2$), 4.25 (s, br, 1H, NH), 5.71 (s, 1H, 5-H), 6.63 (d, 1H, *J*=8.1 Hz, 1-H), 6.70 (d, 1H, *J*=8.1 Hz, 2-H), 6.98 (m, 1H, 6'-H), 7.34 (m, 1H, 7'-H), 7.42 (d, 1H, *J*=8.1 Hz, 4'-H), 7.90 (s, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CD_3OD$): 3.43 ($NCH_2CH(CH_2CH_2)$), 6.33 ($NCH_2CH(CH_2CH_2)$), 6.91 ($NCH_2CH(CH_2CH_2)$), 25.10 ($CH_2$), 25.69 ($CH_2$), 26.98 ($CH_2$), 29.68 ($CH_2$), 30.26 ($CH_2$), 40.32 ($CH_2$), 42.07 ($CH_2$), 47.56 (16-C), 47.95 (13-C), 58.88 (18-C), 63.54 (9-C), 73.64 (14-C), 84.86 (5-C), 110.13 (C), 113.84 (CH), 118.37 (CH), 119.33 (CH), 120.69 (CH), 122.37 (CH), 122.69 (C), 126.79 (C), 128.53 (C), 130.27 (C), 132.45 (C), 138.14 (C), 142.03 (C), 144.74 (C), 157.53 (NCNN); MS (FAB): *m/z* = 543 (M+H); $C_{31}H_{38}N_6O_3$ requires 542; Anal. ($C_{31}H_{38}N_6O_3$:4HCl:3$H_2O$) requires C 50.14 %, H : 6.51 %, N : 11.31 %, found C 50.15 %, H : 6.39 %, N : 11.25 %; mp > 220°C

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-6-aminohexyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (100)**

**97** (mixture of mono and di-BOC-protected products) (140 mg, 0.18 mmol) was dissolved in a mixture conc. HCl/methanol (2.5 mL/2.5 mL). The solution was stirred overnight at room temperature then the solvent was removed until dryness. The solid was washed several times with diethyl ether then dried under vacuum, yielding **100** (HCl salt) as a brown solid (95 mg, 96%).

IR $\nu_{max}$/cm (KBr): 3400 (br, bonded OH and NH), 2936 (br, N-H), 1634 (C=N, NH and $NH_2$); $^1$H NMR (270 MHz, $CD_3OD$): 0.49-0.63 (m, 2H, $NCH_2CH(CHHCHH)$), 0.71-0.91 (m, 2H, $NCH_2CH(CHHCHH)$), 1.09-1.23 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.34-1.49 (m, 4H, 2x$CH_2$), 1.57-1.76 (m, 4H, 2x$CH_2$), 2.94 (t, 2H, *J*=7.3 Hz, $CH_2$), 4.27 (s, br, 1H, NH), 5.71 (s, 1H, 5-H), 6.68 (d, 1H, *J*=8.4 Hz, 1-H), 6.75 (d, 1H, *J*=8.4 Hz, 2-H), 6.95-6.99 (m, 1H, 6'-H), 7.29-7.34 (m, 1H, 7'-H), 7.46 (d, 1H, *J*=8.4 Hz, 4'-H), 7.92 (s, br, 1H, NH); $^{13}$C NMR (67.8 MHz, $CD_3OD$): 3.45 ($NCH_2CH(CH_2CH_2)$), 6.33 ($NCH_2CH(CH_2CH_2)$), 6.91 ($NCH_2CH(CH_2CH_2)$), 25.10 ($CH_2$), 26.97 ($CH_2$), 27.08 ($CH_2$), 28.30 ($CH_2$), 29.64 ($CH_2$), 30.22 ($CH_2$), 40.61 ($CH_2$), 42.58 ($CH_2$), 47.51 (16-C), 47.95 (13-C), 58.86 (18-C), 63.46 (9-C), 73.66 (14-C), 84.85 (5-C), 110.12 (C), 113.97 (CH), 118.25 (CH), 119.32 (CH), 120.76 (CH), 122.32 (CH), 122.77 (C), 126.85 (C), 128.47 (C), 130.28 (C), 132.42 (C), 138.04 (C), 141.95 (C), 144.69 (C), 157.46 (NCNN); MS (FAB): *m/z* = 571 (M+H); $C_{33}H_{42}N_6O_3$

requires 570; Anal. ($C_{33}H_{42}N_6O_3$:4HCl:$3H_2O$) requires C 51.43 %, H : 6.80 %, N : 10.90 %, found C 51.40 %, H : 6.56 %, N : 11.00 %; mp > 220°C

**1,3-Bis-*tert*-butoxycarbonyl-1-acetyl-2-methyl-2-thiopseudourea (104)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (0.87 g, 3.0 mmol), sodium hydride (0.36 g, 9.0 mmol), 18-crown-6 (50 mg) and acetyl chloride (0.51 mL, 6.0 mmol) in dry THF (5 mL) were reacted according to the general procedure B. After purification by silica gel column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, **104** was isolated as a white solid (0.17 g, 19%).

IR $\nu_{max}$/cm (neat): 1750 (carbamate), 1727 (C=N), 1629 (carbamate); $^1$H NMR (400 MHz, $CDCl_3$): 1.44 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 2.42 (s, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 14.95 ($SCH_3$), 24.80 ($CH_3$), 27.08 ($C(CH_3)_3$), 27.18 ($C(CH_3)_3$), 81.81 ($C(CH_3)_3$), 84.36 ($C(CH_3)_3$), 149.35 ($COCH_3$), 152.81(CN), 162.04 (CO), 170.82 (CO); $R_f$ (*n*-hexanes/ethyl acetate: 9/1): 0.22; mp : 54°C

**1,3-Bis-*tert*-butoxycarbonyl-1-allyl-2-methyl-2-thiopseudourea (105)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (0.87 g, 3.0 mmol), sodium hydride (0.36 g, 9.0 mmol), 18-crown-6 (50 mg) and allyl bromide (0.51 mL, 6.0 mmol) in dry THF (5 mL) were reacted according to the general procedure B. After purification by silica gel column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, **105** was isolated as a colourless oil (0.60 g, 61%).

IR $\nu_{max}$/cm (neat): 1722 (C=N), 1619 (carbamate); $^1$H NMR (400 MHz, $CDCl_3$): 1.46 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 2.37 (s, 3H, $SCH_3$), 4.12 (d, 2H, $J$=5.8 Hz, $CH_2$), 5.16-5.26 (m, 2H, $CH=CH_2$), 5.83-5.93 (m, 1H, $CH=CH_2$); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 15.48 ($SCH_3$), 27.97 ($2xC(CH_3)_3$), 51.19 ($CH_2$), 81.66 ($C(CH_3)_3$), 82.42 ($C(CH_3)_3$), 117.83 ($CH=CH_2$), 132.95 ($CH=CH_2$), 151.63 (CN), 157.81 (CO), 162.84 (CO); MS (FAB): *m/z* = 331 (M+H); $C_{15}H_{26}N_2O_4S$ requires 330; $R_f$ (*n*-hexanes/ethyl acetate: 9/1): 0.15

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-bromo-2-butenyl)-2-methyl-2-thiopseudourea (106)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (1.74 g, 6.0 mmol), sodium hydride (0.29 g, 7.2 mmol) and 1,4-dibromo-2-butene (1.41 g, 6.6 mmol) in anhydrous DMF (20 mL) were reacted according to the general procedure B. The crude product was purified by flash column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, yielding **106** as a colourless oil (1.25 g, 49 %).

IR $\nu_{max}$/cm (neat): 1743 (C=N); $^1$H NMR (400 MHz, $CDCl_3$): 1.44 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.35 (s, 3H, $CH_3$), 3.91 (t, 2H, *J*=6.6 Hz, $CH_2$), 4.10 (t, 2H, *J*=5.5 Hz, $CH_2$), 5.76-5.92 (m, 2H, C*H*=C*H*); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 15.50 ($SCH_3$), 27.86 (2x$C(CH_3)_3$), 31.68 ($CH_2Br$), 49.56 ($NCH_2$), 81.57 ($C(CH_3)_3$), 82.59 ($C(CH_3)_3$), 129.70 (*C*H=CH), 129.80 (CH=*C*H), 151.34 (CN), 157.62 (CO), 162.42 (CO); MS (FAB): *m/z* = 423 (M+H, $^{79}$Br) and 425 (M+H, $^{81}$Br); $C_{16}H_{27}N_2O_4S^{79}Br$ requires 422 and $C_{16}H_{27}N_2O_4S^{81}Br$ requires 424; $R_f$ (*n*-hexanes/ethyl acetate: 9/1): 0.37

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-chlorobutyryl)-2-methyl-2-thiopseudourea (107)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (0.87 g, 3.0 mmol), sodium hydride (0.36 g, 9.0 mmol) and 4-chlorobutyryl chloride (0.67 mL, 6.0 mmol) in anhydrous DMF (7 mL) were reacted according to the general procedure B. The crude product was purified by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, and **107** was isolated as a colourless oil (0.40 g, 34 %).

IR $\nu_{max}$/cm (neat): 1750 (carbamate), 1728 (C=N), 1629 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 1.47 (s, 9H, $C(CH_3)_3$), 1.52 (s, 9H, $C(CH_3)_3$), 2.13 (virtual quintet, 2H, *J*=6.4 Hz, $CH_2$), 2.46 (s, 3H, $CH_3$), 3.04 (t, 2H, *J*=6.4 Hz, $COCH_2$), 3.63 (t, 2H, *J*=6.4 Hz, $CH_2Cl$); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 16.07 ($SCH_3$), 27.55 ($CH_2$), 28.15 ($C(CH_3)_3$), 28.27($C(CH_3)_3$), 34.62 ($COCH_2$), 44.48 ($CH_2Cl$), 82.86 ($C(CH_3)_3$), 85.48 ($C(CH_3)_3$), 149.00 (CN), 157.18 (CO), 159.97 (CO), 172.18 ($COCH_2$); MS (FAB): *m/z* = 395 (M+H, $^{35}$Cl) and 397 (M+H, $^{37}$Cl); $C_{16}H_{27}N_2O_5S^{35}Cl$ requires 394 and $C_{16}H_{27}N_2O_5S^{37}Cl$ requires 396; $R_f$ (*n*-hexanes/ethyl acetate: 9/1): 0.25

***N*-(4-Bromo-2-butenyl)phthalimide (110)** [202]

A mixture of 1,2-dibromo-2-butene (2.56 g, 12.0 mmol) and potassium phthalimide (2.22 g, 12.0 mmol) in anhydrous DMF (30 mL) was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was quenched by addition of water (10 mL). The precipitate was filtered, washed with water and dried under vacuum. The crude product was purified by column chromatography, eluting with *n*-hexanes/ethyl acetate: 3/1, affording **110** as a white solid (1.72 g, 51 %).

IR $\nu_{max}$/cm (neat): 2926 (C-H aromatic), 1715 (amide); $^1$H NMR (270 MHz, $CDCl_3$): 3.90 (d, 2H, *J*=6.3 Hz, $CH_2Br$), 4.30 (d, 2H, *J*=5.6 Hz, $NCH_2$), 5.78-6.02 (m, 2H, C*H*=C*H*), 7.71-7.77 (m, 2H), 7.84-7.89 (m, 2H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 31.40 ($CH_2Br$), 38.98 ($NCH_2$), 123.49 (CH), 128.54 (*C*H=CH), 130.21 (CH=*C*H), 132.30 (C), 134.13 (CH), 167.17 (CO); MS (FAB): *m/z* = 280 (M+H, $^{79}$Br), 282 (M+H, $^{81}$Br), $C_{12}H_{10}NO_2{}^{79}Br$ requires 279 and $C_{12}H_{10}NO_2{}^{81}Br$ requires 281; $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.45; mp : 95°C (lit.: 95-96°C)[202]

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-phthalimido-2-butenyl)-2-methyl-2-thiopseudourea (111)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (1.93 g, 6.6 mmol), sodium hydride (0.32 g, 8.0 mmol) and **110** (2.05 g, 7.3 mmol) in anhydrous DMF (20 mL) were reacted according to the general procedure B. Purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, afforded **111** as a colourless oil (2.62 g, 80 %).

IR $\nu_{max}$/cm (neat): 2979, 2932 (C-H aromatic), 1717 (C=N), 1615 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 1.43 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.34 (s, 3H, $SCH_3$), 4.09 (d, 2H, *J*=4.6 Hz, $CH_2$), 4.28 (d, 2H, *J*=4.3 Hz, $CH_2$), 5.75-5.82 (m, 2H, C*H*=C*H*), 7.70-7.77 (m, 2H), 7.81-7.88 (m, 2H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 15.90 ($SCH_3$), 28.38 (2x$C(CH_3)_3$), 39.21 ($CH_2$Nphtha), 50.14 ($CH_2N$), 81.92 ($C(CH_3)_3$), 82.71 ($C(CH_3)_3$), 123.36 (CH), 127.73 (CH=CH), 128.87 (CH=CH), 132.37 (C), 134.01 (CH), 151.64 (CN), 157.80 (CO), 162.63 (CO), 167.71 (CO); MS (FAB): *m/z* = 490 (M+H); $C_{24}H_{31}N_3O_6S$ requires 489; $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.41

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-4'-phthalimido-2-butenyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (112)**

**53** (0.43 g, 1.0 mmol), mercury(II) chloride (0.41 g, 1.5 mmol), triethylamine (0.27 mL, 2.0 mmol) and **111** (0.98 g, 2.0 mmol) were reacted according to the general procedure A. After purification, a mixture containing **112** and the mono-BOC protected analogue was obtained as a brown solid (0.23 g, 13%).

Data for **112**:

$^1$H NMR (400 MHz, $CDCl_3$): 0.17 (d, 2H, *J*=4.7 Hz, $NCH_2CH(CHHCHH)$), 0.51-0.62 (d, 2H, *J*=7.4 Hz, $NCH_2CH(CHHCHH)$), 0.84-0.94 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.36 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 3.94-4.32 (m, 4H, $CH_2CH{=}CHCH_2$), 5.67 (s, 1H, 5-H), 5.72-5.95 (m, 2H, CH=CH), 6.43-6.58 (m, 2H, 1-H and 2-H), 6.77 (m, 1H, 6'H), 7.02-7.27 (m, 2H, 4'-H and 7'-H), 7.46-7.68 (m, 4H, Ar); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 4.31 ($NCH_2CH(CH_2CH_2)$), 4.38 ($NCH_2CH(CH_2CH_2)$), 9.85 ($NCH_2CH(CH_2CH_2)$), 23.57 (10-C), 28.24 ($C(CH_3)_3$), 28.49 ($C(CH_3)_3$), 29.19 ($CH_2$), 31.82 ($CH_2$), 39.18 ($CH_2$), 39.31 ($CH_2$), 44.07 (16-C), 48.41 (13-C), 59.93 (18-C), 62.81 (9-C), 73.01 (14-C), 82.30 ($C(CH_3)_3$), 82.85 ($C(CH_3)_3$), 85.60 (5-C), 111.64 (C), 112.37 (CH), 112.92 (CH), 117.97 (CH), 119.43 (CH), 123.44 (CH), 123.56 (CH), 125.24 (C), 127.29 (C), 127.41 (CH), 127.75 (CH), 130.62 (C), 131.11 (C), 132.33 (C), 134.10 (CH), 134.25 (C), 135.78 (C), 139.88 (C), 143.36 (C), 150.08 (CN), 153:39 (CO), 153.81 (CO), 168.27 (CO); $R_f$ (DCM/MeOH/$NH_4OH$: 110/10/1): 0.41

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-4'-phthalimido-2-butenyl)guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (113)**

The above mixture (0.16 g, 0.18 mmol) was dissolved in a mixture of MeOH/conc. HCl (5 mL/5mL) and the solution was heated at 80°C overnight. The solvents were removed by evaporation until dryness. The solid was washed several times with diethyl ether then dried under vacuum to give **113** (HCl salt) as a brown solid (0.12 g, 97%).

IR $\nu_{max}$/cm (KBr): 3393 (br, bonded OH and bonded NH), 1707 (C=N, NH and $NH_2$), 1610 (CO); $^1$H NMR (270 MHz, $CD_3OD$): 0.50-0.61 (m, 2H, $NCH_2CH(CHHCHH)$), 0.73-0.95 (m, 2H, $NCH_2CH(CHHCHH)$), 1.11-1.24 (m, 1H, $NCH_2CH(CH_2CH_2)$), 3.82-3.91 (m, 2H, $CH_2$Nguan), 4.23-4.33 (m, 2H, $CH_2$Nphtha), 5.73 (s, 1H, 5-H), 5.73-5.86 (m, 2H, CH=CH), 6.62 (d, 1H, *J*=8.1 Hz, 1-H), 6.66 (d, 1H, *J*=8.1 Hz, 2-H), 6.94-7.02 (d, 1H, *J*=8.4 Hz, 6'-H), 7.33 (s, 1H, 4'-H), 7.39 (d, 1H, *J*=8.4 Hz, 7'-H), 7.75-7.87 (m, 4H, Ar); $^{13}$C NMR (67.8 MHz, $CD_3OD$): 3.75 ($NCH_2CH(CH_2CH_2)$), 6.64 ($NCH_2CH(CH_2CH_2)$), 7.25 ($NCH_2CH(CH_2CH_2)$), 25.43 (10-C), 30.09 ($CH_2$), 30.66 ($CH_2$), 40.03 ($CH_2$NPhta), 43.72 (16-C), 47.99 ($CH_2$), 49.05 (13-C), 59.25 (18-C), 63.91 (9-C), 73.98 (14-C), 85.19 (5-C), 110.53 (C), 114.26 (CH), 118.67 (CH), 119.83 (CH), 121.12 (CH), 122.78 (CH), 123.10 (C), 124.17 (CH), 127.27 (C), 128.30 (CH), 129.00 (C), 129.38 (CH), 130.74 (C), 132.99 (C), 133.26 (C), 135.49 (CH), 138.69 (C), 142.60 (C), 145.23 (C), 158.00 (CN), 169.74 (CO); MS (FAB): *m/z* = 671 (M+H); $C_{39}H_{38}N_6O_5$ requires 670; mp > 250°C

**3-Phthalimidopropanol (115)** [139,203,204]

A solution of 3-aminopropanol (3.2 mL, 41.5 mmol), *N*-carbethoxy-phthalimide (9.1 g, 41.5 mmol) and triethylamine (5.8 mL, 41.5 mmol) in THF (100 mL) was stirred overnight at room temperature. The solvent was removed by evaporation and the crude oil purified by column chromatography, eluting with *n*-hexanes/ethyl acetate: 1/1. **115** was isolated as a white solid (7.35 g, 86 %).

IR $\nu_{max}$/cm (KBr): 3413 (br, bonded OH), 1722 (C=N), 1604 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 2.15 (virtual quintuplet, 2H, *J*=6.7 Hz, $CH_2$), 3.56 (t, 2H, *J*=6.6 Hz, $CH_2N$), 3.83 (t, 2H, *J*=6.8 Hz, $CH_2O$), 7.69-7.72 (m, 2H), 7.82-7.85 (m, 2H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 31.10 ($CH_2$), 34.23 ($CH_2N$), 58.96 ($CH_2O$), 123.06 (CH), 131.70 (C), 133.86 (CH), 168.59 (CO); MS (FAB): *m/z* = 206.0814 (M); $C_{11}H_{12}NO_3$ requires 206.0817; $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.45; mp : 65 °C

**3-Phthalimidopropyl *p*-toluenesulfonate (116)** [205]

Method A

To a solution of **115** (1.08 g, 5.25 mmol) and pyridine (1.41 mL, 17.5 mmol) in DCM (5 mL) at 0°C was added a solution of *p*-toluenesulfonyl chloride (1.00 g, 5.25 mmol)

in DCM. The reaction mixture was stirred overnight at room temperature. Water was then added and the mixture acidified with conc. HCl (1.0 mL, 12.3 mmol). The aqueous phase was extracted several times with DCM and the organic phase dried over $MgSO_4$ and concentrated under vacuum. Further purification by column chromatography, eluting with DCM, afforded **116** as a white solid (1.18 g, 63%).

Method B

To a solution of **115** (2.16 g, 10.5 mmol) and triethylamine (1.46 mL, 10.5 mmol) in DCM (5 mL) at 0°C was added a solution of *p*-toluenesulfonyl chloride (2.00 g, 10.5 mmol) in DCM. The reaction mixture was stirred at room temperature for 3 hours; water was added, the aqueous phase then extracted several times with DCM and the organic phase dried over $MgSO_4$ and evaporated under vacuum. Similar purification than used in method A afforded **116** as a white solid (2.07 g, 55%)

IR $\nu_{max}$/cm (KBr): 3104-2970 (C-H aromatic), 1698 (C=N), 1615 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 2.03 (virtual quintuplet, 2H, *J*=6.6 Hz, $CH_2$), 2.41 (s, 3H, $CH_3$), 3.71 (t, 2H, *J*=6.9 Hz, $CH_2N$), 4.08 (t, 2H, *J*=6.4 Hz, $CH_2O$), 7.30 (d, 2H, *J*=8.4 Hz), 7.67-7.72 (m, 2H), 7.75 (d, 2H, *J*=8.4 Hz), 7.78-7.81 (m, 2H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 21.68 ($CH_3$), 27.98 ($CH_2$), 34.61 ($CH_2N$), 67.78 ($CH_2O$), 123.34 (CH), 127.98 (CH), 129.88 (CH), 131.97 (C), 134.07 (CH), 144.87 (C), 168.12 (CO); MS (FAB): *m/z* = 360.0915 (M+H); $C_{18}H_{17}NO_5S$ requires 359.0826; $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.31; mp : 164 °C

**1,3-Bis-*tert*-butoxycarbonyl-1-(3'-phthalimidopropyl)-2-methyl-2-thiopseudourea (117)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (0.74 g, 2.56 mmol), sodium hydride (60% in oil, 92 mg, 2.30 mmol) and **116** (0.92 g, 2.56 mmol) in dry DMF (5 mL) were reacted according to the general procedure B. The crude oil was purified by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1. **117** was isolated as a colourless oil (0.60 g, 49%).

IR $\nu_{max}$/cm (neat): 2974, 2933 (C-H aromatic), 1737 (CO), 1716 (br, C=N), 1621 (carbamate), 1146 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.41 (s, 9H, $C(CH_3)_3$), 1.46 (s,

9H, $C(CH_3)_3$), 2.04 (m, 2H, $CH_2$), 2.34 (s, 3H, $CH_3$), 3.54-3.60 (m, 2H, $CH_2$NPhtha), 3.70 (t, 2H, *J*=7.1 Hz, $CH_2N$), 7.66-7.69 (m, 2H), 7.79-7.82 (m, 2H); $^{13}C$ NMR (67.8 MHz, $CDCl_3$): 15.64 ($CH_3$), 28.06 (2x$C(CH_3)_3$), 28.23 ($CH_2$), 35.67 ($CH_2$), 46.71 ($CH_2$), 81.93 ($C(CH_3)_3$), 82.59 ($C(CH_3)_3$), 123.30 (CH), 132.14 (C), 134.02 (CH), 151.70 (CO), 162.82 (NCN), 168.28 (CO); $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.48

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-3'-phthalimido-propyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (118)**

**53** (0.24 g, 0.55 mmol), mercury(II) chloride (0.17 g, 0.60 mmol), triethylamine (0.16 mL, 1.18 mmol) and **117** (0.54 g, 1.13 mmol) were reacted according to the general procedure A. After purification, a mixture containing **118** and the mono-BOC protected analogue was isolated as a brown solid (0.11 g, 23 %).

Data for **118**:

$^1H$ NMR (270 MHz, $CDCl_3$): 0.15 (d, 2H, *J*=4.2 Hz, $NCH_2CH(CHHCHH)$), 0.55 (d, 2H, *J*=7.4 Hz, $NCH_2CH(CHHCHH)$), 0.82-0.93 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.35 (s, 9H, $C(CH_3)_3$), 5.62 (s, 1H, 5-H), 6.48 (d, 1H, *J*=8.0 Hz, 1-H), 6.56 (d, 1H, *J*=8.0 Hz, 2-H), 6.57-6.59 (m, 1H), 7.03-7.17 (m, 1H), 7.52-7.73 (m, 5H); $R_f$ (DCM/ $MeOH/NH_4OH$: 200/10/1): 0.31

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-3'-phthalimido-propyl) guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (120)**

The above mixture (40 mg, 47 μmol) in DCM (2 mL) was treated with trifluoroacetic acid (0.2 mL) as described in the general procedure P. The desired product **120** (TFA salt) was recrystallised from ethanol/diethyl ether and isolated as a brown solid (27 mg, 58%).

$^1H$ NMR (270 MHz, $CD_3OD$): 0.54 (d, 2H, *J*=4.7 Hz, $NCH_2CH(CHHCHH)$), 0.72-0.89 (m, 2H, $NCH_2CH(CHHCHH)$), 1.11-1.21 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.88-2.00 (m, 2H, $CH_2$), 3.73 (t, 2H, *J*=6.5 Hz, $CH_2N$), 4.24 (d, 1H, *J*=5.9 Hz), 5.73 (s, 1H, 5-H), 6.63 (d, 1H, *J*=8.3 Hz, 1-H), 6.67 (d, 1H, *J*=8.3 Hz, 2-H), 7.04 (dd, 1H, *J*=2.0 Hz and *J*=8.6 Hz, 6'-H), 7.39 (d, 1H, *J*=2.0 Hz, 4'-H), 7.44 (d, 1H, *J*=8.6 Hz, 7'-H),

7.76-7.84 (m, 4H); $^{13}$C NMR (67.8 MHz, $CD_3OD$): 3.40 ($NCH_2CH(CH_2CH_2)$), 6.24 ($NCH_2CH(CH_2CH_2)$), 6.88 ($NCH_2CH(CH_2CH_2)$), 25.04 ($CH_2$), 28.93 ($CH_2$), 29.74 ($CH_2$), 30.29 ($CH_2$), 35.95 ($CH_2$), 40.07 ($CH_2$), 47.60 (16-C), 49.84 (13-C), 58.90 (18-C), 63.60 (9-C), 73.63 (14-C), 84.89 (5-C), 110.11 (C), 113.87 (CH), 118.26 (CH), 119.36 (CH), 120.61 (CH), 122.38 (CH), 122.63 (C), 124.16 (CH), 126.91 (C), 128.57 (C), 130.30 (C), 132.50 (C), 133.29 (C), 135.43 (CH), 138.20 (C), 142.11 (C), 144.80 (C), 157.60 (NCNN), 169.90 (CO); Anal. ($C_{38}H_{38}N_6O_5$:3TFA:6$H_2O$) requires C 47.7 %, H : 4.8 %, N : 7.6 %, found C 47.7 %, H : 5.3 %, N : 8.2 %; mp > 220 °C

**_N,N_-Dibenzylaminopropanol (124)** [206]

To a solution of aminopropanol (3.06 mL, 40 mmol) in DCM (5 mL) was added a solution of benzyl bromide (4.75 mL, 40 mmol) in DCM (5 mL). The reaction mixture was stirred overnight at room temperature, then the solution was basified to pH=10 with $NH_4OH$; water was added, the organic phase separated and the aqueous phase further extracted with DCM. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography eluting first with *n*-hexanes, then with *n*-hexanes/ethyl acetate: 6/1, afforded **124** as a colourless oil (2.14 g, 42 %).

IR $\nu_{max}$/cm (neat): 3339 (br, bonded OH), 2945 (C-H aromatic); $^1$H NMR (270 MHz, $CDCl_3$): 1.73-1.79 (m, 2H, $CH_2$), 2.64 (t, 2H, *J*=5.8 Hz, $CH_2N$), 3.56 (s, 4H, 2x$CH_2$Ph), 3.64 (t, 2H, *J*=5.3 Hz, $CH_2O$), 4.67 (s, 1H, OH), 7.23-7.36 (m, 10H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 28.02 ($CH_2$), 53.21 ($CH_2$), 58.64 ($CH_2$), 63.91 ($CH_2$), 127.33 (CH), 128.52 (CH), 129.21 (CH), 138.33 (C); $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.43

**_N,N_-Dibenzylaminopropyl _p_-toluenesulfonate (125)**

**124** (1.28 g, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol) and *p*-toluenesulfonyl chloride (0.95 g, 5.0 mmol) in DCM (5 mL) were reacted according to a similar way as employed for the preparation of **116** (method B). **125** (0.84 g, 39%) was isolated as an off-white solid.

IR $\nu_{max}$/cm (neat): 3442 (br, bonded OH), 2922 (C-H aromatic), 1187 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.78 (virtual quintuplet, 2H, *J*=6.7 Hz, $CH_2$), 2.41 (s, 3H, $CH_3$), 2.43 (t, 2H, *J*=6.7 Hz, $CH_2N$), 3.46 (s, 4H, 2x$CH_2Ph$), 4.03 (t, 2H, *J*=6.8 Hz, $CH_2O$), 7.21-7.31 (m, 12H), 7.72 (d, 2H, *J*=8.4 Hz); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 14.35 ($CH_2$), 21.34 ($CH_3$), 59.23 ($CH_2$), 64.65 ($CH_2$), 126.00 (CH), 128.73 (C), 128.76 (CH), 129.36 (CH), 130.42 (CH), 132.59 (CH), 139.40 (C), 143.79 (C); mp > 220 °C

**1,3-Bis-*tert*-butoxycarbonyl-1-(*N*,*N*-dibenzylaminopropyl)-2-methyl-2-thiopseudourea (126)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (0.64 g, 2.21 mmol), sodium hydride (60% in oil, 88 mg, 2.20 mmol), 15-crown-5 (40 µL, 0.22 mmol) and **125** (1.04 g, 2.44 mmol) in dry DMF (5 mL) were reacted according to the general procedure B. **126** was isolated as a colourless oil (0.82 g, 71%).

$^1$H NMR (270 MHz, $CDCl_3$): 1.42 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.83-1.94 (m, 2H), 2.32 (s, 3H, $CH_3$), 2.42 (t, 2H, *J*=6.8 Hz, $CH_2N$), 3.53 (s, 4H, 2x$CH_2Ph$), 3.53 (m, 2H, $CH_2NCN$), 7.18-7.36 (m, 10H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 15.53 ($CH_3$), 26.36 ($CH_2$), 28.04 ($C(CH_3)_3$), 28.09 ($C(CH_3)_3$), 47.53 ($CH_2$), 50.78 ($CH_2$), 58.18 (2x$CH_2$), 81.69 ($C(CH_3)_3$), 82.20 ($C(CH_3)_3$), 126.85 (CH), 128.21 (CH), 128.85 (CH), 139.60 (C), 151.79 (CO), 157.87 (CO), 163.11 (NCN); $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.64

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-3',3'-dibenzylamino propyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (131)**

**53** (0.13 g, 0.30 mmol), mercury(II) chloride (0.12 g, 0.43 mmol), triethylamine (0.08 mL, 0.56 mmol) and **126** (0.31 g, 0.59 mmol) were reacted according to the general procedure A. After purification, a mixture containing **127** and the mono-BOC protected derivative was isolated as a brown solid (0.13 g, 48%). MS (FAB): *m/z* = 909 (M+H); $C_{54}H_{64}N_6O_7$ requires 908; $R_f$ (DCM/MeOH/$NH_4OH$: 200/10/1): 0.31

The above mixture (66 mg, 73 µmol) in DCM (3 mL) was treated with trifluoroacetic acid (0.2 mL) as described in the general procedure P and **131** (TFA salt) was isolated as an off-white solid (70 mg, 82%).

$^1$H NMR (270 MHz, $CD_3OD$): 0.54 (d, 2H, *J*=4.2 Hz, $NCH_2CH(CHHCHH)$), 0.74-0.91 (m, 2H, $NCH_2CH(CHHCHH)$), 1.11-1.21 (m, 1H, $NCH_2CH(CH_2CH_2)$), 4.37 (s, 4H, $2xCH_2Ph$), 5.73 (s, 1H, 5-H), 6.65 (d, 1H, *J*=8.2 Hz, 1-H), 6.67 (d, 1H, *J*=8.2 Hz, 2-H), 6.93 (dd, 1H, *J*=1.9 Hz and *J*=8.6 Hz, 6'-H), 7.29 (d, 1H, *J*=1.9 Hz, 4'-H), 7.44 (d, 1H, *J*=8.6 Hz, 7'-H); $^{13}$C NMR (67.8 MHz, $CD_3OD$): 3.34 ($NCH_2CH(CH_2CH_2)$), 6.20 ($NCH_2CH(CH_2CH_2)$), 6.81 ($NCH_2CH(CH_2CH_2)$), 24.49 ($CH_2$), 24.99 ($CH_2$), 29.68 ($CH_2$), 30.23 ($CH_2$), 39.61 ($CH_2$), 47.56 (16-C), 50.68 ($CH_2$), 58.48 ($2xCH_2Ph$), 58.90 (18-C), 63.62 (9-C), 73.57 (14-C), 84.86 (5-C), 110.05 , 113.84, 118.26, 119.36, 120.63, 122.32, 122.57, 126.71, 128.54, 130.27, 130.47, 130.83, 131.20, 132.18, 132.53, 138.21, 142.13, 144.78, 157.56 (NCNN); mp : 188 °C; Anal. ($C_{44}H_{48}N_6O_3$:3TFA:$2H_2O$) requires C 55.25 %, H 5.10 %, N 7.73 %, found: C 55.3 %, H 4.92 %, N 7.60 %

**1,3-Bis-*tert*-butoxycarbonyl-1-(5'-iodopentyl)-2-methyl-2-thiopseudourea (132)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (2.95 g, 10.1 mmol), sodium hydride (60% in oil, 0.41 g, 10.2 mmol), 15-crown-5 (0.2 mL, 1 mmol) and 1,5-diiodopentane (4.5 mL, 33.5 mmol) in dry DMF (5 mL) were reacted according to the general procedure B, but the reaction mixture was stirred at room temperature overnight. **132** was isolated as a colourless oil (2.50 g, 51%).

IR $\nu_{max}$/cm (neat): 2977, 2932 (C-H aromatic), 1719 (C=N), 1618 (carbamate), 1143 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.30-1.40 (m, 2H), 1.46 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.61-1.72 (m, 2H), 1.83 (virtual quintuplet, 2H, *J*=7.2 Hz), 2.37 (s, 3H, $SCH_3$), 3.16 (t, 2H, *J*=6.9 Hz, $CH_2I$), 3.48 (m, 2H, $CH_2N$); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 6.59 ($CH_2I$), 15.55 ($CH_3$), 27.60 ($CH_2$), 27.70 ($CH_2$), 27.98 ($C(CH_3)_3$), 28.05 ($C(CH_3)_3$), 32.93 ($CH_2$), 48.56 ($CH_2N$), 81.79 ($C(CH_3)_3$), 82.25 ($C(CH_3)_3$), 151.85 (CO), 157.83 (CO), 162.79 (NCN); MS (FAB): *m/z* = 486.9 (M); $C_{17}H_{31}IN_2O_4S$ requires 486.410; $R_f$ (*n*-hexanes/ethyl acetate: 5/1): 0.65

**1,3-Bis-*tert*-butoxycarbonyl-1-(5'-nitropentyl)-2-methyl-2-thiopseudourea (133)**

A solution of sodium nitrite (2.16 g, 3.08 mmol) and **132** (0.90 g, 1.86 mmol) in a mixture of DMF (5 mL) and water (1 mL) was stirred for 2 hrs at room temperature.

Water was added and the aqueous solution extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent removed under vacuum. Purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, afforded **133** as a colourless oil (0.30 g, 40%).

IR $\nu_{max}$/cm (neat): 2978, 2934 (C-H aromatic), 1719 (C=N), 1617 (carbamate), 1143 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.36-1.46 (m, 2H), 1.46 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 1.65-1.76 (m, 2H), 2.03 (virtual quintuplet, 2H, *J*=7.3 Hz), 2.37 (s, 3H, $SCH_3$), 3.47-3.53 (m, 2H, $CH_2$NBoc), 4.37 (t, 2H, *J*=6.9 Hz, $CH_2NO_2$); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 15.60 ($CH_3$), 23.39 ($CH_2$), 26.89 ($CH_2$), 28.00 ($C(CH_3)_3$), 28.07 ($C(CH_3)_3$), 48.22 ($CH_2$NCN), 75.42 ($CH_2NO_2$), 81.93 ($C(CH_3)_3$), 82.45 ($C(CH_3)_3$), 151.85 (CO), 157.85 (CO), 162.67 (NCN); $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.64

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-5'-nitropentyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (134)**

**53** (0.30 g, 0.71 mmol), mercury(II) chloride (0.28 g, 0.99 mmol), triethylamine (0.20 mL, 1.41 mmol) and **133** (0.57 g, 1.41 mmol) were reacted according to the general procedure A. After purification, a mixture containing **134** and its mono-BOC protected analogue was isolated as a brown solid (0.18 g, 32%).

IR $\nu_{max}$/cm (neat): 3394 (br, bonded OH and NH), 2976, 2931 (C-H aromatic), 1707 (C=N), 1614 (carbamate), 1148 (C-N); $^1$H NMR (270 MHz, $CDCl_3$) (data for di-BOC protected derivative): 0.14 (d, 2H, *J*=4.3 Hz, $NCH_2CH(CHHCHH)$), 0.54 (d, 2H, *J*=7.9 Hz, $NCH_2CH(CHHCHH)$), 0.83-0.92 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.37 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 5.64 (s, 1H, 5-H), 6.48 (d, 1H, *J*=8.0 Hz, 1-H), 6.53-6.59 (m, 1H), 6.76-6.81 (m, 1H), 7.02-7.16 (m, 2H); $^1$H NMR (270 MHz, $CDCl_3$) (data for mono-BOC protected derivative): 0.14 (d, 2H, *J*=4.2 Hz, $NCH_2CH(CHHCHH)$), 0.55 (d, 2H, *J*=7.6 Hz, $NCH_2CH(CHHCHH)$), 0.81-0.93 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.13 (s, 9H, $C(CH_3)_3$), 5.59 (s, 1H, 5-H), 6.46 (d, 1H, *J*=8.2 Hz, 1-H), 6.56 (d, 1H, *J*=8.2 Hz, 2-H), 6.74-6.85 (m, 1H), 7.02-7.10 (m, 2H); MS (FAB): *m/z* = 687 (M+H), 787 (M+H); P (mono-BOC protected derivative) $C_{37}H_{46}N_6O_7$ requires 686; P (di-BOC protected derivative) $C_{42}H_{54}N_6O_9$ requires 786; $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.46

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-5'-aminopentyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (135)**

Method A

The above mixture (50 mg, 64 μmol) and iron(II)sulfate heptahydrate (0.16 g, 0.58 mmol) in methanol (2 mL), water (0.5 mL) and concentrated ammonia (1 mL) were reacted according to the same procedure as employed for the preparation of **53**. After purification by column chromatography, eluting first with $CHCl_3$, then with $CHCl_3$/MeOH/$NH_4OH$: 250/10/1, a mixture containing **135** and its mono-BOC protected analogue was isolated as a brown solid (21 mg, 43 %).

Method B

To a suspension of palladium (10 wt. % on activated carbon) (40 mg, 38 μmol) in dry methanol (1.5 mL) were added **134** (and its mono-BOC protected derivative) (60 mg, 76 μmol) and ammonium formate (60 mg, 0.95 mmol). The solution was refluxed for 2 hrs, after which the solid was removed by filtration and the solvent evaporated. The crude product was purified by column chromatography, eluting first with $CHCl_3$: 100%, then with gradient elution ($CHCl_3$/MeOH/$NH_4OH$: 500/10/1 to $CHCl_3$/MeOH/$NH_4OH$: 250/10/1). A mixture containing **135** and its mono-BOC protected analogue was isolated as a brown solid (17 mg, 29%).

IR $\nu_{max}$/cm (neat): 3529 (br, bonded OH and NH), 2926 (C-H aromatic), 1717 (C=N), 1611 (carbamate), 1145 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 0.14 (d, 2H, *J*=4.7 Hz, $NCH_2CH(CHHCHH)$), 0.55 (d, 2H, *J*=8.4 Hz, $NCH_2CH(CHHCHH)$), 0.84-0.96 (m, 4H), 3.77 (t, 1H), 5.63 (s, 1H, 5-H), 6.42-6.60 (m, 3H, 1-H + 2-H + Ar), 6.89-6.92 (m, 1H), 7.08-7.14 (m, 1H), 7.97-8.02 (br, m, 1H); MS (FAB): *m/z* = 757 (M+H); $C_{42}H_{56}N_6O_7$ requires 756; $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.43

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-5'-isothiocyanatopentyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (136)**

**135** and its mono-BOC protected analogue (12 mg, 16 μmol), sodium hydrogencarbonate (8.0 mg, 95 μmol) and thiophosgene (1.3 μL, 17 μmol) were

reacted according to the general procedure N. After purification, a mixture containing **136** and the mono-BOC analogue was isolated as a white solid (9 mg, 71%).

Data for **136**:

IR $\nu_{max}$/cm (neat): 3329 (br, bonded OH and NH), 2183 and 2106 (isothiocyanate), 1704 (C=N, NH and $NH_2$), 1644 and 1613 (carbamate); $^1$H NMR (270 MHz, $CDCl_3$): 0.14 (d, 2H, *J*=4.7 Hz, $NCH_2CH(CHHCHH)$), 0.55 (d, 2H, *J*=7.9 Hz, $NCH_2CH(CHHCHH)$), 0.83-0.94 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.37 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 5.65 (s, 1H, 5-H), 6.51 (d, 1H, *J*=8.0 Hz, 1-H), 6.57 (d, 1H, *J*=8.0 Hz, 2-H), 6.80 (s, 1H, 6'-H), 6.99-7.18 (m, 2H, 4'-H + 7'-H), 9.13 (s, br, 1H, NH); $R_f$ (DCM/MeOH: 10/1): 0.51

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(*N*'-5'-isothiocyanatopentyl) guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (137)**

The above mixture (**136** and its mono-BOC protected analogue) (12.7 mg, 15.9 μmol) in DCM (2 mL) was treated with trifluoroacetic acid (0.2 mL) as described in the general procedure P. **137** (TFA salt) was isolated as a white solid (6.9 mg, 46%).

IR $\nu_{max}$/cm (neat): 3342 (br, bonded OH and NH), 2184 and 2105 (isothiocyanate), 1704 (C=N, NH and $NH_2$); $^1$H NMR (270 MHz, $CD_3OD$): 0.54 (d, 2H, *J*=3.7 Hz, $NCH_2CH(CHHCHH)$), 0.76-0.92 (m, 2H, $NCH_2CH(CHHCHH)$), 1.11-1.22 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.93-2.02 (m, 2H, $CH_2$), 3.58 (t, 2H, *J*=6.5 Hz, $CH_2$), 4.23 (d, 1H, *J*=6.1 Hz, CH), 5.73 (s, 1H, 5-H), 6.64 (d, 1H, *J*=8.2 Hz, 1-H), 6.68 (d, 1H, *J*=8.2 Hz, 2-H), 7.01-7.06 (m, 1H, 6'-H), 7.34-7.36 (m, 1H, 4'-H), 7.46 (dd, 1H, *J*=2.2 Hz and *J*=8.6 Hz, 7'-H); MS (FAB): *m/z* = 599.2822 (M+H); $C_{33}H_{39}N_6O_3S$ requires 599.2804; mp > 250°C

**1,3-Bis-*tert*-butoxycarbonyl-1-allyl-2-methyl-2-thiopseudourea (138)**

1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (3.86 g, 13.3 mmol), sodium hydride (60% in oil, 0.52 g, 12.9 mmol), 15-crown-5 (0.26 mL, 13 mmol) and diiodopropane (4.58 mL, 39.9 mmol) were reacted according to the general procedure B, but the reaction mixture was stirred overnight at room temperature. **138** was isolated as a colourless oil (2.04 g, 47 %)

IR $\nu_{max}$/cm (neat): 3084 (CH, alkene), 1722 (C=N), 1618 (carbamate), 1144 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.44 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.35 (s, 3H, $SCH_3$), 4.11 (td, 2H, *J*=1.4 and *J*=5.9 Hz, $CH_2NBOC$), 5.13-5.26 (m, 2H), 5.79-5.93 (m, 1H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 15.55 ($CH_3$), 28.02 ($C(CH_3)_3$), 28.04 ($C(CH_3)_3$), 51.26 ($CH_2$), 81.74 ($C(CH_3)_3$), 82.51 ($C(CH_3)_3$), 117.90 ($CH_2$), 133.01 (CH), 151.59 (CO), 157.86 (CO), 162.98 (CN); MS (FAB): *m/z* = 331.1695 (M+H); $C_{15}H_{27}N_2O_4S$ requires 331.1691; $R_f$ (*n*-hexanes/ethyl acetate: 5/1): 0.57

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-bromobutyl)-2-methyl-2-thiopseudourea (140)**
1,3-Bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (2.95 g, 10.2 mmol), sodium hydride (60% in oil, 0.41 g, 10.2 mmol), 15-crown-5 (0.2 mL, 1.0 mmol) and 1,4-dibromobutane (4.0 mL, 33.5 mmol) in dry DMF (5 mL) were reacted according to the general procedure B, but the reaction mixture was stirred overnight at room temperature. **140** was isolated as a colourless oil (2.07 g, 48%).

IR $\nu_{max}$/cm (neat): 2979, 2932 (C-H aromatic), 1720 (C=N), 1648 (carbamate), 1139 (C-N); $^1$H NMR (270 MHz, $CDCl_3$): 1.45 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 1.76-1.90 (m, 4H), 2.36 (s, 3H, $SCH_3$), 3.39 (t, 2H, *J*=6.4 Hz, $CH_2Br$), 3.52 (t, 2H, *J*=7.2 Hz, $CH_2NBOC$); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 15.17 ($SCH_3$), 27.20 ($CH_2$), 27.61 ($C(CH_3)_3$), 27.66 ($C(CH_3)_3$), 29.52 ($CH_2$), 32.64 ($CH_2$), 47.47 ($CH_2N$), 81.30 ($C(CH_3)_3$), 81.92 ($C(CH_3)_3$), 151.35 (CO), 157.34 (CO), 162.15 (NCN); $R_f$ (*n*-hexanes/ethyl acetate: 3/1): 0.69

**1,3-Bis-*tert*-butoxycarbonyl-1-(4'-nitrobutyl)-2-methyl-2-thiopseudourea (141)**
A solution of sodium nitrite (2.74 g, 4.70 mmol) and **140** (1.00 g, 2.35 mmol) in DMF (5 mL) was stirred for 16 hrs at room temperature. Water was then added and the solution extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent removed under vacuum. Purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, afforded **141** (0.17 g, 19%). The reaction was repeated with DMF/$H_2O$: 5/1 as the solvent mixture and the yield improved to 36%.

$^1$H NMR (270 MHz, $CDCl_3$): 1.45 (s, 9H, $C(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.65-1.78 (m, 2H), 1.95-2.06 (m, 2H), 2.36 (s, 3H, $SCH_3$), 3.55 (t, 2H, *J*=7.2 Hz, $CH_2NBOC$), 4.39 (t, 2H, *J*=6.9 Hz, $CH_2NO_2$); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 15.46 ($SCH_3$), 24.31 ($CH_2$), 25.53 ($CH_2$), 27.85 ($C(CH_3)_3$), 27.90 ($C(CH_3)_3$), 47.47 ($CH_2NCN$), 74.89 ($CH_2NO_2$), 81.85 ($C(CH_3)_3$), 82.54 ($C(CH_3)_3$), 151.71 (CO), 157.67 (CO), 162.29 (NCN)

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-4'-nitrobutyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (142)**

**53** (0.17 g, 0.43 mmol), mercury(II) chloride (0.18 g, 0.65 mmol), triethylamine (0.12 mL, 0.86 mmol) and **141** (0.18 g, 0.43 mmol) were reacted according to the general procedure A. The reaction mixture was stirred at 60°C for 48 hours. After purification, a mixture containing **142** and its mono-BOC protected derivative was isolated as a yellowish solid (91 mg, 27%).

$^1$H NMR (270 MHz, $CDCl_3$): 0.15 (d, 2H, *J*=4.2 Hz, $NCH_2CH(CHHCHH)$), 0.56 (d, 2H, *J*=8.2 Hz, $NCH_2CH(CHHCHH)$), 0.84-0.93 (m, 1H, $NCH_2CH(CH_2CH_2)$), 1.36 (s, 9H, $C(CH_3)_3$), 1.48 (s, 9H, $C(CH_3)_3$), 3.80 (t, 2H, *J*=7.3 Hz, $CH_2NBoc$), 4.14 (s, br, 1H, NH), 4.38 (t, 2H, *J*=6.6 Hz, $CH_2NO_2$), 5.63 (s, 1H, 5-H), 6.50 (d, 1H, *J*=7.7 Hz, 1-H), 6.54-6.60 (m, 1H, 2-H), 6.78-6.82 (m, 1H, 6'-H), 7.04-7.18 (m, 2H, 7'-H and 4'-H), 8.66 (s, br, 1H, NH); $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.46

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-*tert*-butoxycarbonyl-(*N*'-4'-aminobutyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (143)**

A suspension of the above mixture (**142** and its mono-BOC protected derivative) (40 mg, 52 μmol), palladium (10 wt. % on activated carbon) (33 mg, 31 μmol) and ammonium formate (64 mg, 1.01 mmol) in dry methanol (5 mL) were reacted according to the same procedure as used for the preparation of **135** (method B). A mixture containing **143** and its mono-BOC protected analogue was isolated as a brown solid (8 mg, 21%).

IR $\nu_{max}$/cm (neat): 3320 (br, bonded OH and NH), 2926 (C-H aromatic), 1700 (C=N); $^1$H NMR (270 MHz, $CDCl_3$ for **143**): 0.15 (d, 2H, *J*=4.7 Hz, $NCH_2CH(CHHCHH)$),

0.56 (d, 2H, *J*=6.9 Hz, $NCH_2CH(CH\mathit{H}CH\mathit{H})$), 0.81-0.93 (m, 1H, $NCH_2C\mathit{H}(CH_2CH_2)$), 1.40 (s, 9H, $C(CH_3)_3$), 1.49 (s, 9H, $C(CH_3)_3$), 3.32-3.38 (m, 1H), 5.64 (s, 1H, 5-H), 6.43-6.61 (m, 2H, 1-H and 2-H), 6.75-6.81 (m, 1H, 6'-H), 6.96-7.16 (m, 2H, 7'-H and 4'-H); $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.44; MS (FAB): *m/z* = 643 (M+H), 743 (M+H); P (mono-BOC protected derivative) $C_{36}H_{46}N_6O_5$ requires 642; P (di-BOC protected derivative) $C_{41}H_{54}N_6O_7$ requires 742

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(benzylimino) [7,7'-bimorphinan]-3,3',14,14'-tetrol (152)**

NorBNI **(13)** (0.30g, 0.45 mmol), sodium hydride (0.18g, 4.52 mmol), 18-crown-6 (30 mg, 0.11 mmol) and benzyl bromide (0.16 mL, 1.36 mmol) were treated according to the general procedure I, the reaction being carried out however at room temperature and for 43 hours. The crude oil was purified by column chromatography, eluting with DCM/MeOH/$NH_4OH$: 400/10/1 to 290/10/1, to yield a mixture of tri- and pentabenzyl-substituted norBNI (0.33g). This mixture was dissolved in MeOH/conc. HCl (20 mL, 1/1) and heated to 90°C for 40 h. Cooling, basification ($NH_4OH$) and removal of the precipitate by filtration, was followed by evaporation of the filtrate to dryness. Column chromatography, eluting with DCM/MeOH/$NH_4OH$: 200/10/1, yielded BnorBNI **(152)** as an off-white solid (0.21g, 63%).

IR $\nu_{max}$/cm (KBr): 3401 (br); $^1$H NMR (400 MHz, $CDCl_3$): 0.09 (d, 4H, *J*=5.1 Hz, $2xNCH_2CH(C\mathit{H}HC\mathit{H}H)$), 0.49 (d, 4H, *J*=8.2 Hz, $2xNCH_2CH(CH\mathit{H}CH\mathit{H})$), 0.78-0.83 (m, 2H, $2xNCH_2C\mathit{H}(CH_2CH_2)$), 3.02 (d, 2H, *J*=18.3 Hz, 10-H + 10'-H), 3.16 (d, 2H, *J*=5.9 Hz, 9-H + 9'-H), 5.27 (d, 1H, *J*=15.8 Hz, $NCH\mathit{H}$), 5.33 (s, 2H, 5-H +5'-H), 5.51 (d, 1H, *J*=15.8 Hz, $NCH\mathit{H}$), 6.42 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.49 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 6.88-6.90 (m, 2H, Ar), 7.22-7.29 (m, 3H, Ar); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.79 ($2xNCH_2CH(CH_2\mathit{C}H_2)$), 3.90 ($2xNCH_2CH(CH_2\mathit{C}H_2)$), 9.40 ($2xNCH_2\mathit{C}H(CH_2CH_2)$), 22.99 (10-C + 10'-C), 28.98 (8-C + 8'-C), 31.44 (15-C + 15'-C), 43.55 (16-C + 16'-C), 47.27 ($CH_2$), 48.06 (13-C + 13'-C), 59.34 (18-C + 18'-C), 62.37 (9-C + 9'-C), 72.72 (14-C + 14'-C), 85.00 (5-C + 5'-C), 116.44 (7-C + 7'-C), 116.76 (2-C + 2'-C), 118.61 (1-C + 1'-C), 125.29 (11-C + 11'-C), 125.50 (CH), 125.63 (6-C + 6'-C), 126.81 (CH), 128.62 (CH), 130.72 (12-C + 12'-C), 138.63 (3-C + 3'-C), 140.33 (C), 142.89 (4-C + 4'-C); MS (FAB): *m/z* = 752.3715 (M+H), $C_{47}H_{50}N_3O_6$ requires 752.3698; $R_f$ (DCM/MeOH/$NH_4OH$: 110/10/1): 0.76; mp >

240°C; Anal. ($C_{47}H_{49}N_3O_6$:2HCl:$5H_2O$) requires C 61.73 %, H 6.72 %, N 4.59 %, found : C 62.06 %, H 6.95 %, N 4.76 %

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-isothiocyanatobenzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (161)**

**205** (15 mg, 20 μmol), sodium hydrogencarbonate (9.8 mg, 117 μmol) and thiophosgene (1.6 μL, 21 μmol) were reacted according to the general procedure N. After purification, **161** was isolated as a white solid (7 mg, 44%).

IR $\nu_{max}$/cm (neat): 3294 (br, bonded OH), 2111 (isothiocyanate); $^1$H NMR (270 MHz, $CDCl_3$): 0.10 (d, 4H, *J*=4.2 Hz, $NCH_2CH(CHHCHH)$), 0.47-0.52 (m, 4H, $NCH_2CH(CHHCHH)$), 0.76-0.88 (m, 2H, $NCH_2CH(CH_2CH_2)$), 1.58 (d, 2H, *J*=8.6 Hz), 3.03 (d, 2H, *J*=18.5 Hz), 3.16 (d, 2H, *J*=5.2 Hz), 5.24 (d, 1H, *J*=17.1 Hz, NCHHPh), 5.27 (s, 2H, 5-H + 5'-H), 5.41 (d, 1H, *J*=17.1 Hz, NCHHPh), 6.48 (d, 2H, *J*=8.3 Hz, 1-H + 1'-H), 6.58 (d, 2H, *J*=8.3 Hz, 2-H + 2'-H), 6.69-6.74 (m, 1H), 7.01 (s, 1H), 7.09-7.14 (m, 1H), 7.21-7.27 (m, 1H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.79 ($2xNCH_2CH(CH_2CH_2)$), 3.91 ($2xNCH_2CH(CH_2CH_2)$), 9.32 ($2xNCH_2CH(CH_2CH_2)$), 23.03 (10-C + 10'-C), 28.94 (8-C + 8'-C), 31.40 (15-C + 15'-C), 43.53 (16-C + 16'-C), 46.85 ($CH_2$), 48.06 (13-C + 13'-C), 59.30 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.61 (14-C + 14'-C), 84.83 (5-C + 5'-C), 116.78 (CH), 118.74 (CH), 123.25 (CH), 124.45 (CH), 124.84 (CH), 125.26 (C), 125.57 (C), 129.82 (CH), 130.54 (C), 131.50 (C), 135.06 (NCS), 138.62 (C), 141.52 (C), 142.71 (C); MS (FAB): *m/z* = 808.3351 (M), 809.3359 (M+H); $C_{48}H_{49}N_4O_6S$ requires 809.3372; $R_f$ (DCM/MeOH: 10/1): 0.44; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(4-(isothiocyanatomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (163)**

**169** (16 mg, 21 μmol), sodium hydrogencarbonate (10.3 mg, 122 μmol) and thiophosgene (1.7 μL, 21 μmol) were reacted according to the general procedure N. After purification, **163** was isolated as a white solid (15 mg, 89%).

IR $\nu_{max}$/cm (neat): 3385 (br, bonded OH), 2179 and 2096 (isothiocyanate); $^1$H NMR (270 MHz, $CDCl_3$): 0.09 (d, 4H, *J*=4.3 Hz, $2xNCH_2CH(CHHCHH)$), 0.49 (d, 4H,

*J*=7.9 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.75-0.88 (m, 2H, 2xNCH$_2$C*H*(CHHCHH)), 3.02 (d, 2H, *J*=18.5 Hz), 3.15 (d, 2H, *J*=5.9 Hz), 4.67 (s, 2H, CH$_2$NCS), 5.27 (d, 1H, *J*=17.1 Hz, NC*H*HPh), 5.29 (s, 2H, 5-H + 5'-H), 5.47 (d, 1H, *J*=17.1 Hz, NCH*H*Ph), 6.47 (d, 2H, *J*=8.1 Hz, 1-H + 1'-H), 6.56 (d, 2H, *J*=8.1 Hz, 2-H + 2'-H), 6.90 (d, 2H, *J*=8.2 Hz, Ar), 7.23 (d, 2H, *J*=8.2 Hz, Ar); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 3.77 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.89 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 9.31 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 23.01 (10-C + 10'-C), 28.95 (8-C + 8'-C), 31.37 (15-C + 15'-C), 43.51 (16-C + 16'-C), 47.02 (NCH$_2$), 48.02 (13-C + 13'-C), 48.29 (*C*H$_2$NCS), 59.29 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.66 (14-C + 14'-C), 84.87 (5-C + 5'-C), 116.59 (C), 116.72 (CH), 118.67 (CH), 125.21 (C), 125.60 (C), 126.20 (CH), 127.17 (CH), 130.67 (C), 131.98 (NCS), 132.85 (C), 138.63 (C), 140.19 (C), 142.75 (C); MS (FAB): *m/z* = 822.3418 (M), 823.3495 (M+H); $C_{49}H_{50}N_4O_6S$ requires 822.3451; $R_f$ (DCM/MeOH: 10/1): 0.43; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-(isothiocyanatomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (164)**

**170** (11 mg, 14 μmol), sodium hydrogencarbonate (7.1 mg, 84 μmol) and thiophosgene (1.2 μL, 15 μmol) were reacted according to the general procedure N. After purification, **164** was isolated as a white solid (8 mg, 70%).

IR $\nu_{max}$/cm (neat): 3303 (br, bonded OH), 2165 and 2096 (isothiocyanate); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 3.80 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.91 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 9.33 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 23.06 (10-C + 10'-C), 28.95 (8-C + 8'-C), 31.43 (15-C + 15'-C), 43.50 (16-C + 16'-C), 47.09 (NCH$_2$), 48.01 (13-C + 13'-C), 48.44 (*C*H$_2$NCS), 59.31 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.74 (14-C + 14'-C), 84.92 (5-C + 5'-C), 116.62 (CH), 116.68 (C), 118.74 (CH), 124.07 (CH), 125.32 (C), 125.43 (CH), 125.62 (C), 125.68 (CH), 129.13 (CH), 130.74 (C), 131.14 (NCS), 135.06 (C), 138.55 (C), 140.87 (C), 142.77 (C); $R_f$ (DCM/MeOH: 10/1): 0.43; mp (oxalate salt) > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(2-(isothiocyanatomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (165)**

**171** (20 mg, 26 μmol), sodium hydrogencarbonate (19 mg, 226 μmol) and thiophosgene (2.1 μL, 28 μmol) were reacted according to the general procedure N. After purification, **165** was isolated as a white solid (7.4 mg, 35%).

IR $\nu_{max}$/cm (neat): 3370 (br, bonded OH), 2161 and 2094 (isothiocyanate); $^1$H NMR (270 MHz, $CDCl_3$): 0.09 (d, 4H, *J*=4.4 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.46-0.52 (m, 4H, 2xNCH$_2$CH(CH*H*CH*H*)), 0.75-0.87 (m, 2H, 2xNCH$_2$C*H*(CHHCHH)), 3.02 (d, 2H, *J*=18.3 Hz), 3.15 (d, 2H, *J*=6.4 Hz), 4.84 (d, 1H, *J*=16.2 Hz, C*H*HNCS), 4.92 (d, 1H, *J*=16.2 Hz, CH*H*NCS), 5.23 (d, 1H, *J*=17.3 Hz, NC*H*HPh), 5.29 (s, 2H, 5-H + 5'-H), 5.52 (d, 1H, *J*=17.3 Hz, NCH*H*Ph), 6.35 (d, 1H, *J*=6.9 Hz), 6.50 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.57 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 7.21-7.41 (m, 3H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.79 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.90 (2xNCH$_2$CH(CH$_2$*C*H$_2$)), 9.38 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 23.03 (10-C + 10'-C), 28.97 (8-C + 8'-C), 31.43 (15-C + 15'-C), 43.52 (16-C + 16'-C), 44.49 (CH$_2$), 46.73 (CH$_2$), 48.10 (13-C + 13'-C), 59.33 (18-C + 18'-C), 62.34 (9-C + 9'-C), 72.64 (14-C + 14'-C), 84.80 (5-C + 5'-C), 116.74 (CH), 116.88 (C), 118.77 (CH), 125.28 (C), 125.68 (C), 126.23 (CH), 127.46 (CH), 128.01 (CH), 129.48 (CH), 130.18 (C), 130.60 (C), 132.48 (NCS), 137.69 (C), 138.57 (C), 142.71 (C); MS (FAB): *m/z* = 822.3449 (M), 823.3537 (M+H); $C_{49}H_{51}N_4O_6S$ requires 823.3529; $R_f$ (DCM/MeOH: 10/1): 0.44; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-aminobenzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (167)**

**198** (60 mg, 56 μmol) was dissolved in a mixture of conc. HCl/MeOH (5mL, 1/1) and the reaction was stirred overnight at 85°C. The solvents were then removed and water was added. The aqueous phase was basified to pH=8 with diluted $NH_4OH$ and extracted with DCM/MeOH: 5/1. The organic phase was dried ($MgSO_4$) and the solvent evaporated. Purification by column chromatography, eluting first with $CHCl_3$/MeOH/$NH_4OH$: 450/10/1, then with $CHCl_3$/MeOH/$NH_4OH$: 300/10/1, afforded **203** (34 mg, 68%). **203** (29 mg, 32 μmol) and hydrazine hydrate (3.0 μL, 96 μmol) in ethanol (1 mL) were reacting according to the general procedure O. **167** was isolated as a brown solid (22 mg, 90%).

IR $\nu_{max}$/cm (neat): 3368 (br, bonded OH and NH); $^1$H NMR (270 MHz, $CDCl_3$): 0.08-0.10 (m, 4H, $NCH_2CH(CHHCHH)$), 0.48-0.51 (m, 4H, $NCH_2CH(CHHCHH)$), 0.79-0.88 (m, 2H, $NCH_2CH(CH_2CH_2)$), 3.02 (d, 2H, *J*=18.3 Hz), 3.15 (d, 2H, *J*=6.1 Hz), 5.17 (d, 1H, *J*=17.0 Hz, NC*H*H), 5.35 (s, 2H, 5-H + 5'-H), 5.39 (d, 1H, *J*=17.0 Hz, NCH*H*), 6.09 (s, 1H), 6.44 (d, 2H, *J*=8.0 Hz, 1-H + 1'-H), 6.46-6.57 (m, 2H), 6.55 (d, 2H, *J*=8.0 Hz, 2-H + 2'-H), 7.08 (t, 1H, *J*=7.8 Hz); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 3.76 ($2xNCH_2CH(CH_2CH_2)$), 3.90 ($2xNCH_2CH(CH_2CH_2)$), 9.35 ($2xNCH_2CH(CH_2CH_2)$), 23.00 (10-C + 10'-C), 28.94 (8-C + 8'-C), 31.41 (15-C + 15'-C), 43.54 (16-C + 16'-C), 47.28 ($NCH_2$), 48.01 (13-C + 13'-C), 59.31 (18-C + 18'-C), 62.30 (9-C + 9'-C), 72.75 (14-C + 14'-C), 84.88 (5-C + 5'-C), 112.76 (CH), 113.84 (CH), 116.08 (CH), 116.17 (C), 117.30 (CH), 118.55 (CH), 125.37 (C), 125.71 (C), 129.20 (CH), 130.80 (C), 138.62 (C), 140.84 (C), 143.28 (C), 146.72 (C); MS (FAB): *m/z* = 767 (M+H); $C_{47}H_{50}N_4O_6$ requires 766; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.25; mp > 250°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(4-(aminomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (169)**

**227** (39 mg, 43 μmol) in ethanol (1 mL) and hydrazine hydrate (6.3 μL, 202 μmol) were reacted according to the general procedure O. **169** was isolated as a brown solid (18 mg, 54%).

$^1$H NMR (270 MHz, $CDCl_3$): 0.05 (d, 4H, *J*=5.0 Hz, $2xNCH_2CH(CHHCHH)$), 0.39-0.50 (m, 4H, $2xNCH_2CH(CHHCHH)$), 0.68-0.79 (m, 2H, $2xNCH_2CH(CH_2CH_2)$), 3.00 (d, 2H, *J*=18.3 Hz), 3.15 (d, 2H, *J*=6.2 Hz), 3.62 (s, 2H, $CH_2NH_2$), 3.72-4.18 (br, s, 2H, $NH_2$), 5.22 (d, 1H, *J*=16.8 Hz, NC*H*H), 5.27 (s, 2H, 5-H + 5'-H), 5.43 (d, 1H, *J*=16.8 Hz, NCH*H*), 6.46 (d, 2H, *J*=8.0 Hz, 1-H + 1'-H), 6.57 (d, 2H, *J*=8.0 Hz, 2-H + 2'-H), 6.80 (d, 2H, *J*=7.6 Hz), 7.12 (d, 2H, *J*=7.6 Hz); $^{13}$ C NMR (67.8 MHz, $CDCl_3$): 3.62 ($2xNCH_2CH(CH_2CH_2)$), 3.96 $2xNCH_2CH(CH_2CH_2)$), 9.32 ($2xNCH_2CH(CH_2CH_2)$), 22.98 (10-C + 10'-C), 28.97 (8-C + 8'-C), 31.46 (15-C + 15'-C), 43.65 (16-C + 16'-C), 45.32 ($CH_2NH_2$), 47.06 ($NCH_2$), 48.01 (13-C + 13'-C), 59.29 (18-C + 18'-C), 62.22 (9-C + 9'-C), 72.73 (14-C + 14'-C), 84.56 (5-C + 5'-C), 116.40 (C), 117.24 (CH), 118.66 (CH), 124.56 (C), 125.57 (C), 126.15 (CH), 127.62 (CH), 130.66 (C), 138.30 (C), 139.32 (C), 140.76 (C), 142.94 (C); MS (FAB): *m/z* =

781.3952 (M+H); $C_{48}H_{53}N_4O_6$ requires 781.3864; $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.34; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-(aminomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (170)**

**228** (32 mg, 35 μmol) in ethanol (1 mL) and hydrazine hydrate (4.4 μL, 141 μmol) were reacted according to the general procedure O. **170** was isolated as a brown solid (13 mg, 47%).

IR $\nu_{max}$/cm (neat): 3419 (br, bonded OH and NH), 1640 (N-H); $^{13}C$ NMR (67.8 MHz, $CDCl_3$): 3.73 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.91 (2xNCH$_2$CH(CH$_2$*C*H$_2$)), 9.34 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 23.01 (10-C + 10'-C), 28.96 (8-C + 8'-C), 31.57 (15-C + 15'-C), 43.59 (16-C + 16'-C), 45.30 ($CH_2$), 47.66 ($CH_2$), 47.99 (13-C + 13'-C), 59.30 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.73 (14-C + 14'-C), 84.63 (5-C + 5'-C), 116.14 (C), 118.10 (CH), 118.46 (CH), 125.00 (C), 125.86 (CH), 125.91 (CH), 126.44 (CH), 128.29 (CH), 130.76 (C), 139.14 (C), 141.81 (C), 143.92 (C); $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.35; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(2-(aminomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (171)**

**229** (30 mg, 33 μmol) in ethanol (1 mL) and hydrazine hydrate (5.0 μL, 160 μmol) were reacted according to the general procedure O. **171** was isolated as a brown solid (22 mg, 86%).

IR $\nu_{max}$/cm (neat): 3353 and 3076 (br, bonded OH and NH); $^1H$ NMR (270 MHz, $CDCl_3$): 0.04 (d, 4H, *J*=4.4 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.44 (d, 4H, *J*=8.0 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.68-0.80 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 3.06 (d, 2H, *J*=6.2 Hz), 3.29 (d, 1H, *J*=14.1 Hz, C*H*HNH$_2$), 3.77 (d, 1H, *J*=14.1 Hz, CH*H*NH$_2$), 4.95 (s, 2H, 5-H + 5'-H), 5.24 (d, 1H, *J*=15.0 Hz, NC*H*H), 5.44 (d, 1H, *J*=15.0 Hz, NCH*H*), 6.38 (d, 2H, *J*=8.1 Hz, 1-H + 1'-H), 6.50 (d, 2H, *J*=8.1 Hz, 2-H + 2'-H), 7.10 (d, 1H, *J*=7.2 Hz), 7.21-7.32 (m, 2H), 7.49 (d, 1H, *J*=7.2 Hz); $^{13}C$ NMR (67.8 MHz, $CDCl_3$/$CD_3OD$: 8/1): 3.64 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.73 (2xNCH$_2$CH(CH$_2$*C*H$_2$)), 9.18 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 22.81 (10-C + 10'-C), 28.70 (8-C + 8'-C), 31.43 (15-C

+ 15'-C), 42.14 ($CH_2$), 43.36 (16-C + 16'-C), 47.50 ($CH_2$ or 13-C + 13'-C), 47.60 ($CH_2$ or 13-C + 13'-C), 59.19 (18-C + 18'-C), 62.14 (9-C + 9'-C), 72.59 (14-C + 14'-C), 84.19 (5-C + 5'-C), 116.20 (C), 117.56 (CH), 118.57 (CH), 124.04 (C), 126.03 (C), 127.39 (CH), 128.64 (CH), 129.74 (CH), 130.57 (C), 131.93 (CH), 134.13 (C), 139.64 (C), 141.31 (C), 142.84 (C); MS (FAB): *m/z* = 781 (M+H); $C_{48}H_{52}N_4O_6$ requires 780; $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.37; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-3-(4-nitrobenzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-3,14,14'-triol (172)**

NorBNI (**13**) (0.66 g, 1.0 mmol), sodium hydride (60% in oil, 0.40 g, 10.0 mmol), 18-crown-6 (20 mg, 0.08 mmol) and 4-nitrobenzyl chloride (0.51 g, 3.0 mmol) in dry THF (20 mL) were reacted according to the general procedure I. **172** (0.08 g, 10 %) and **173** (0.28 g, 30 %) were isolated as brown solids, but no desired product could be isolated.

$^1$H NMR (270 MHz, $CDCl_3$): 0.07-0.12 (m, 4H, 2xNCH$_2$CH(C*H*HC*H*H)), 0.51-0.53 (m, 4H, 2xNCH$_2$CH(CH*H*CH*H*)), 0.79-0.91 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 5.04 (d, 1H, *J*=13.2 Hz, OC*H*H), 5.18 (d, 1H, *J*=13.2 Hz, OCH*H*), 5.52 (s, 1H, 5-H or 5'-H), 5.62 (s, 1H, 5-H or 5'-H), 6.47-6.55 (m, 3H, 1-H + 1'-H + 2-H or 2'-H), 6.64 (d, 1H, *J*=8.2 Hz, 2-H or 2'-H), 7.44 (d, 2H, *J*=8.6 Hz), 8.11 (d, 2H, *J*=8.6 Hz), 8.82 (br, s, 1H, NH); $R_f$ (DCM/MeOH/$NH_4OH$: 200/20/1): 0.29

**17,17'-Bis(cyclopropylmethyl)-3,3'-(4-nitrobenzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-14,14'-diol (173)**

Obtained as a side product from the reaction that gave **172** (brown solid).

$^1$H NMR (270 MHz, $CDCl_3$): 0.08 (d, 4H, *J*=4.7 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.49 (d, 4H, *J*=7.9 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.73-0.88 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 5.07 (d, 2H, *J*=13.4 Hz, 2xOC*H*H), 5.24 (d, 2H, *J*=13.4 Hz, 2xOCH*H*), 5.45 (s, 2H, 5-H + 5'-H), 6.45 (d, 2H, *J*=8.1 Hz, 1-H + 1'-H), 6.54 (d, 2H, *J*=8.1 Hz, 2-H + 2'-H), 7.42 (d, 4H, *J*=8.1 Hz), 8.14 (d, 4H, *J*=8.1 Hz), 8.32 (br, s, 1H, NH), $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.56 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.76 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 9.21 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 22.93 (10-C + 10'-C), 28.66

(8-C + 8'-C), 31.34 (15-C + 15'-C), 43.30 (16-C + 16'-C), 47.49 (13-C + 13'-C), 58.97 (18-C + 18'-C), 61.84 (9-C + 9'-C), 69.66 (2x$OCH_2$), 72.27 (14-C + 14'-C), 85.19 (5-C + 5'-C), 116.26 (C), 116.39 (CH), 118.40 (CH), 123.38 (CH), 124.59 (C), 126.91 (C), 127.74 (CH), 131.50 (C), 141.06 (C), 144.65 (C), 147.14 (C); $R_f$ (DCM/MeOH/$NH_4OH$: 200/12/1): 0.16

**17,17'-Bis(cyclopropylmethyl)-3,3'-(3-nitrobenzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-14,14'-diol (175)**

Isolated as a side product from the reaction that afforded **176** (brown solid).

$^1$H NMR (270 MHz, $CDCl_3$): 0.13 (d, 4H, *J*=4.2 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.48-0.55 (m, 4H, 2xNCH$_2$CH(CH*H*CH*H*)), 0.77-0.90 (m, 2H, 2xNCH$_2$C*H*($CH_2CH_2$)), 3.04 (d, 2H, *J*=18.5 Hz, 10-H + 10'-H), 3.18 (d, 2H, *J*=5.7 Hz, 9-H + 9'-H), 5.05 (d, 2H, *J*=11.9 Hz, 2xOC*H*H), 5.12 (d, 2H, *J*=11.9 Hz, 2xOCH*H*), 5.45 (s, 2H, 5-H + 5'-H), 6.48 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.66 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 7.24-7.42 (m, 8H), 8.10 (br, s, 1H); MS (FAB): *m/z* = 932 (M); $C_{54}H_{53}N_5O_{10}$ requires 932

**17,17'-Bis(cyclopropylmethyl)-3,3'-(3-nitrobenzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-nitrobenzylimino)[7,7'-bimorphinan]-14,14'-diol (176)**

NorBNI **(13)** (0.10 g, 0.15 mmol), sodium hydride (60% in oil, 66 mg, 1.65 mmol) and 3-nitrobenzyl bromide (0.108 g, 0.50 mmol) in dry DMF (5 mL) were reacted according to the general procedure I. **176** (45 mg, 28 %) was isolated as a brown solid.

$^1$H NMR (270 MHz, $CDCl_3$): 0.10 (d, 4H, *J*=4.2 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.51 (d, 4H, *J*=7.9 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.77-0.89 (m, 2H, 2xNCH$_2$C*H*($CH_2CH_2$)), 4.96 (s, 4H, $OCH_2$), 5.26 (s, 2H, 5-H + 5'-H), 5.44 (d, 1H, *J*=17.3 Hz, NC*H*H), 5.54 (d, 1H, *J*=17.3 Hz, NCH*H*), 6.54 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.64 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 7.11-7.25 (m, 2H), 7.45-7.58 (m, 4H), 7.71 (d, 1H, *J*=8.4 Hz), 7.93 (s, 1H), 8.15 (d, 2H, *J*=7.9 Hz), 8.19 (s, 2H); MS (FAB): *m/z* = 1067 (M); $C_{61}H_{58}N_6O_{12}$ requires 1067; $R_f$ (DCM/MeOH/$NH_4OH$: 200/12/1): 0.18

**17,17'-Bis(cyclopropylmethyl)-3,3'-(benzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-14,14'-diol (177)**

A solution of norBNI **(13)** (0.15 g, 0.23 mmol), benzyl bromide (0.14 mL, 1.13 mmol) and potassium carbonate (0.10 g, 0.68 mmol) in dry DMF (2 mL) was stirred at room temperature for 22 hrs. Water (3 mL) was then added, the organic phase isolated and the aqueous phase further extracted with DCM. The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography, eluting first with 100% DCM, then with DCM/MeOH/$NH_4OH$: 450/10/1, which afforded **177** as a brown solid (0.18 g, 94 %).

$^1H$ NMR (400 MHz, $CDCl_3$): 0.12 (d, 4H, *J*=4.3 Hz, 2x$NCH_2CH(CHHCHH)$), 0.52 (d, 4H, *J*=8.2 Hz, 2x$NCH_2CH(CHHCHH)$), 0.83-0.90 (m, 2H, 2x$NCH_2CH(CH_2CH_2)$), 3.05 (d, 2H, *J*=18.8 Hz), 3.18 (d, 2H, *J*=6.2 Hz), 5.07 (d, 2H, *J*=11.9 Hz, 2x$OCHH$), 5.12 (d, 2H, *J*=11.9 Hz, 2x$OCHH$), 5.46 (s, 2H, 5-H + 5'-H), 6.48 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.65 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 7.27-7.42 (m, 10 H), 8.11 (br, s, 1H, NH); MS (FAB): *m/z* = 842 (M); $C_{54}H_{55}N_3O_6$ requires 842; $R_f$ (DCM/MeOH/$NH_4OH$: 290/10/1): 0.49

**17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-tetraacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (178)** [102]

NorBNI **(13)** (0.62 g, 0.93 mmol) was dissolved in acetic anhydride (15 mL) and the solution was stirred for two hours at 100°C under a nitrogen atmosphere. Excess of acetic anhydride was then removed under vacuum and the residual oil was basified to pH=7 with $NH_4OH$. The aqueous phase was extracted with DCM and the organic phase washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by column chromatography, eluting first with $CHCl_3$ then with $CHCl_3$/MeOH/$NH_4OH$: 450/10/1, afforded **178** as an off-white solid (0.75 g, 97%).

IR $\nu_{max}$/cm (KBr): 3348 (br, bonded NH), 1770 and 1729 (CO); $^1H$ NMR (270 MHz, $CDCl_3$): 0.01-0.06 (m, 4H, $NCH_2CH(CHHCHH)$), 0.42-0.45 (m, 4H, $NCH_2CH(CHHCHH)$), 0.68-0.76 (m, 2H, $NCH_2CH(CH_2CH_2)$), 1.88 (s, 6H, 2x$CH_3$), 2.19 (s, 6H, 2x$CH_3$), 3.09 (d, 2H, *J*=18.8 Hz, 10-H and 10'-H), 3.17 (d, 2H, *J*=16.6 Hz, 8-H and 8'-H), 4.43 (d, 2H, *J*=5.9 Hz, 9-H and 9'-H), 5.48 (s, 2H, 5-H and 5'-H),

6.61 (d, 2H, *J*=8.2 Hz, 1-H and 1'-H), 6.75 (d, 2H, *J*=8.2 Hz, 2-H and 2'-H), 8.39 (br, s, 1H, NH); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.53 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.68 (2xNCH$_2$CH(CH$_2$*C*H$_2$)), 9.40 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 20.49 (2xCH$_3$), 22.40 (2xCH$_3$), 23.79 (10-C + 10'-C), 24.37 (8-C + 8'-C), 30.91 (15-C + 15'-C), 43.49 (16-C + 16'-C), 48.05 (13-C + 13'-C), 55.77 (9-C + 9'-C), 59.44 (18-C + 18'-C), 84.04 (14-C + 14'-C), 85.81 (5-C + 5'-C), 115.44 (7-C + 7'-C), 118.36 (1-C + 1'-C), 121.98 (2-C + 2'-C), 124.21 (6-C + 6'-C), 130.86 (12-C + 12'-C), 132.00 (11-C + 11'-C), 132.45 (3-C + 3'-C), 146.89 (4-C + 4'-C), 168.58 (CO), 170.97 (CO); MS (FAB): *m/z* = 830.3638 (M+H); $C_{48}H_{52}N_3O_{10}$ requires 830.2652; $R_f$ (DCM/MeOH/$NH_4OH$: 200/12/1): 0.26; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-3,3'-(4-cyanobenzyloxy)-14,14'-diacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (179)**

**178** (0.25 g, 0.30 mmol), sodium hydride (60% in oil, 0.12 g, 3.00 mmol), 18-crown-6 (10 mg, 0.04 mmol) and α-bromo-*p*-tolunitrile (0.12 g, 6.12 mmol) in dry THF (10 mL) were reacted according to the general procedure I. **179** (0.10 g, 33 %) was isolated as a brown solid, but no desired product could be isolated.

$^1$H NMR (270 MHz, $CDCl_3$): 0.02-0.07 (m, 4H, NCH$_2$CH(C*H*HC*H*H)), 0.44-0.47 (m, 4H, NCH$_2$CH(CH*H*CH*H*)), 0.67-0.81 (m, 2H, NCH$_2$C*H*(CH$_2$CH$_2$)), 1.95 (s, 6H, 2xCH$_3$), 4.43 (d, 2H, *J*=5.7 Hz, 9-H and 9'-H), 5.10 (d, 2H, *J*=13.1 Hz, 2xOC*H*H), 5.21 (d, 2H, *J*=13.1 Hz, 2xOCH*H*), 5.90 (s, 2H, 5-H and 5'-H), 6.57 (d, 2H, *J*=8.2 Hz, 1-H and 1'-H), 6.69 (d, 2H, *J*=8.2 Hz, 2-H and 2'-H), 7.45 (d, 4H, *J*=8.3 Hz), 7.63 (d, 4H, *J*=8.3 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.53 (NCH$_2$CH(*C*H$_2$CH$_2$)), 3.90 (NCH$_2$CH(CH$_2$*C*H$_2$)), 9.55 (NCH$_2$*C*H(CH$_2$CH$_2$)), 22.58 (2xCH$_3$), 23.47 (10-C + 10'-C), 24.78 (8-C + 8'-C), 26.08 (CH$_3$), 31.55 (15-C + 15'-C), 43.55 (16-C + 16'-C), 47.90 (13-C + 13'-C), 55.56 (9-C + 9'-C), 59.59 (18-C + 18'-C), 71.39 (2xOCH$_2$), 82.57 (14-C + 14'-C), 85.23 (5-C + 5'-C), 111.57 (C), 118.16 (CH), 118.72 (C), 118.98 (CH), 121.41 (C), 126.93 (C), 127.69 (4xCH), 128.14 (C), 130.83 (C), 132.22 (4xCH), 141.19 (C), 143.02 (C), 144.56 (C), 169.81 (NCO), 170.87 (2xCO); MS (FAB): *m/z* = 1018 (M); $C_{62}H_{59}N_5O_9$ requires 1018; $R_f$ (DCM/MeOH/$NH_4OH$: 250/5/1):0.27

**17,17'-Bis(cyclopropylmethyl)-3,3'-(3-nitrobenzyloxy)-14,14'-diacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (180)**

**178** (0.20 g, 0.24 mmol), sodium hydride (60% in oil, 41 mg, 1.03 mmol) and 3-nitrobenzyl bromide (0.10 g, 0.48 mmol) in dry THF (6 mL) were reacted according to the general procedure I. **180** (70 mg, 29 %) was isolated as a brown solid, but no desired product could be isolated.

$^1$H NMR (270 MHz, $CDCl_3$): 0.01-0.08 (m, 4H, $NCH_2CH(CHHCHH)$), 0.44 (d, 4H, *J*=7.4 Hz, $NCH_2CH(CHHCHH)$), 0.68-0.78 (m, 2H, $NCH_2CH(CH_2CH_2)$), 1.56 (d, 2H, *J*=10.7 Hz), 1.79 (s, 3H, $CH_3$), 1.80 (s, 3H, $CH_3$), 3.04 (d, 2H, *J*=18.5 Hz), 3.24 (d, 2H, *J*=16.6 Hz), 4.43 (d, 2H, *J*=5.7 Hz), 4.81-5.02 (m, 4H, $2xOCH_2$), 5.33 (s, 2H, 5-H and 5'-H), 6.39 (d, 2H, *J*=8.3 Hz, 1-H and 1'-H), 6.44 (d, 2H, *J*=8.3 Hz, 2-H and 2'-H), 7.40 (virtual double triplet, 2H, *J*=1.5 and 7.9 Hz), 7.64 (d, 2H, *J*=7.4 Hz), 8.09 (d, 2H, *J*=8.2 Hz), 8.21-8.24 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.45 ($2xNCH_2CH(CH_2CH_2)$), 3.87 ($2xNCH_2CH(CH_2CH_2)$), 9.52 ($2xNCH_2CH(CH_2CH_2)$), 22.42 ($2xCH_3$), 23.56 (10-C + 10'-C), 24.62 (8-C + 8'-C), 31.19 (15-C + 15'-C), 43.50 (16-C + 16'-C), 48.07 (13-C + 13'-C), 55.85 (9- C + 9'-C), 59.51 (18- C + 18'-C), 70.13 ($2xOCH_2$), 83.99 (14-C + 14'-C), 84.93 (5-C + 5'-C), 115.76 (C), 116.08 (CH), 118.48 (CH), 122.70 (CH), 122.77 (CH), 124.65 (C), 127.88 (C), 129.27 (CH), 130.51 (C), 133.73 (CH), 139.29 (C), 141.14 (C), 144.47 (C), 148.15 (C), 170.68 (CO); $R_f$ (DCM/MeOH/$NH_4OH$: 500/10/1): 0.22

**17,17'-Bis(cyclopropylmethyl)-3,3'-(3-nitrobenzyloxy)-14,14'-diacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-nitrobenzylimino)[7,7'-bimorphinan] (181)**

**180** (70 mg, 69 µmol), sodium hydride (60% in oil, 29 mg, 0.72 mmol) and 3-nitrobenzyl bromide (47 mg, 0.22 mmol) in dry THF (5 mL) were reacted according to the general procedure I. **181** (32 mg, 40 %) was isolated as a brown solid.

IR $\nu_{max}$/cm (neat): 1762 and 1731 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 0.01-0.07 (m, 4H, $NCH_2CH(CHHCHH)$), 0.43 (d, 4H, *J*=6.9 Hz, $NCH_2CH(CHHCHH)$), 0.67-0.77 (m, 2H, $NCH_2CH(CH_2CH_2)$), 1.87 (s, 6H, $2xCH_3$), 4.44 (d, 2H, *J*=5.9 Hz), 4.86 (s, 4H, $2xOCH_2$), 5.19 (s, 2H, 5-H and 5'-H), 5.40 (d, 1H, *J*=17.6 Hz, NCHH), 5.48 (d, 1H, *J*=17.6 Hz, NCHH), 6.57 (d, 2H, *J*=7.9 Hz, 1-H + 1'-H), 6.61-6.64 (m, 2H, 2-H +

2'-H), 7.23-7.27 (m, 2H), 7.42-7.68 (m, 6H), 8.06-8.15 (m, 4H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.47 (2x$NCH_2CH(CH_2CH_2)$), 3.93 (2x$NCH_2CH(CH_2CH_2)$), 9.58 (2x$NCH_2CH(CH_2CH_2)$), 22.42 (2x$CH_3$), 23.67 (10-C + 10'-C), 24.77 (8-C + 8'-C), 31.28 (15-C + 15'-C), 43.49 (16-C + 16'-C), 46.80 ($NCH_2PhNO_2$), 48.18 (13-C + 13'-C), 55.99 (9- C + 9'-C), 59.56 (18- C + 18'-C), 70.46 (2x$OCH_2$), 83.93 (14-C + 14'-C), 84.30 (5-C + 5'-C), 116.51 (C), 117.01 (CH), 118.86 (CH), 120.62 (CH), 121.70 (CH), 122.21 (CH), 122.76 (CH), 125.48 (C), 128.24 (C), 128.81 (CH), 129.30 (CH), 130.75 (C), 131.57 (CH), 133.15 (CH), 139.41 (C), 141.19 (C), 141.64 (C), 144.61 (C), 148.26 (C), 148.57 (C), 170.82 (CO); $R_f$ (DCM/MeOH/$NH_4OH$: 250/5/1): 0.33

**4-Phthalimidobenzyl bromide (182)**

Method A

A solution of imidazole (80 mg, 1.16 mmol) and triphenylphosphine (0.30 g, 1.16 mmol) in DCM (5 mL) was cooled down to 0°C under a nitrogen atmosphere. Bromine (60 µL, 1.16 mmol) was added dropwise and the reaction mixture was stirred for 10 minutes. A solution of **190** (0.18 g, 0.53 mmol) in DCM (1 mL) was then added and the reaction mixture allowed to warm up to room temperature and stirred for a further 3 hrs. Water was added and the aqueous phase extracted several times with DCM. The organic phase was dried ($MgSO_4$) and the solvent evaporated. Purification by flash chromatography, eluting with *n*-hexanes/ethyl acetate: 4/1, gave **182** as a white solid (0.10 g, 60%).

Method B.

Bromine (0.18 mL, 3.51 mmol), triphenylphosphine (0.95 g, 3.62 mmol) and **194** (1.14 g, 3.10 mmol) were treated as described for the preparation of **184**, which afforded **182** (0.53 g, 54%) as a white solid.

Method C.

To a solution of $NaBrO_3$ (6.75 g, 45 mmol) in water (22.5 mL) was added **244** (3.55 g, 15 mmol) in ethyl acetate (30 mL). Stirring was continued for 10 minutes after which a solution of $NaHSO_3$ (4.65 g, 45 mmol) in water (45 mL) was added dropwise. The reaction mixture was stirred for 6 hours at room temperature then poured into 200

mL of diethyl ether. The organic phase was collected and the aqueous phase further extracted with diethyl ether. The combined organic phase was washed with a solution of sodium hydrogensulfite, dried ($MgSO_4$) and concentrated under vacuum. **182** was isolated as a white solid after recrystallisation in acetone (2.94 g, 62%).

IR $\nu_{max}$/cm (KBr): 2920, 2859 (C-H aromatic), 1707 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 4.52 (s, 2H, $CH_2$), 7.43 (d, 2H, *J*=8.5 Hz), 7.52 (d, 2H, *J*=8.5 Hz), 7.77-7.80 (m, 2H), 7.93-7.96 (m, 2H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 32.63 ($CH_2$), 123.89 (CH), 126.73 (CH), 129.88 (CH), 131.68 (C), 134.58 (CH), 137.52 (C), 167.15 (CO); MS (FAB): *m/z* = 315.9960 (M+H, $^{79}$Br) and 317.9945 (M+H, $^{81}$Br); $C_{15}H_{11}{}^{79}BrNO_2$ requires 315.9972; $C_{15}H_{11}{}^{81}BrNO_2$ requires 317.9952; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.17, (*n*-hexanes/ethyl acetate: 1/1): 0.70; mp : 205°C

**3-Phthalimidobenzyl bromide (183)**

Bromine (0.15 mL, 2.81 mmol), triphenylphosphine (0.77 g, 2.93 mmol) and **195** (0.85 g, 2.45 mmol) were treated as described for the preparation of **182**, affording **183** as a white solid (0.58 g, 75%).

$^1$H NMR (270 MHz, $CDCl_3$): 4.52 (s, 2H, $CH_2$), 7.36-7.50 (m, 4H), 7.77-7.80 (m, 2H), 7.93-7.96 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 32.53 ($CH_2$), 123.74 (CH), 126.29 (CH), 126.90 (CH), 128.55 (CH), 129.44 (CH), 131.53 (C), 131.97 (C), 134.46 (CH), 138.74 (C), 166.98 (CO); MS (FAB): *m/z* = 315.9971 (M+H, $^{79}$Br) and 317.9954 (M+H, $^{81}$Br); $C_{15}H_{11}{}^{79}BrNO_2$ requires 315.9972; $C_{15}H_{11}{}^{81}BrNO_2$ requires 317.9952; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.33

**2-Phthalimidobenzyl bromide (184)** [207]

A solution of triphenylphosphine (0.145 g, 55 μmol) in DCM (1 mL) was cooled to 0°C under a nitrogen atmosphere. Bromine (30 μL, 55 μmol) was added dropwise and the reaction mixture stirred for 10 minutes. A solution of **196** (0.160 g, 46 μmol) in DCM (1 mL) was added and the reaction mixture allowed to warm up to room temperature and stirred for a further 3 hrs. Water was then added, and the aqueous phase extracted several times with DCM. The organic phase was dried ($MgSO_4$) and

the solvent evaporated. Purification by flash chromatography, eluting with *n*-hexanes/ethyl acetate: 4/1, gave **184** as a white solid (0.10 g, 69 %).

IR $\nu_{max}$/cm (KBr): 3049-2995 (C-H aromatic), 1714 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 4.35 (s, 2H, $CH_2$), 7.17-7.21 (m, 1H), 7.37-7.41 (m, 1H), 7.43-7.50 (m, 1H), 7.79-7.82 (m, 2H), 7.95-7.98 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 29.43 ($CH_2$), 123.89 (CH), 129.74 (CH), 129.79 (CH), 130.81 (C), 131.07 (CH), 131.82 (C), 134.45 (CH), 135.76 (CN), 167.16 (CO); MS (FAB): *m/z* = 315.9970 (M+H, $^{79}$Br) and 317.9959 (M+H, $^{81}$Br); $C_{15}H_{10}{}^{79}BrNO_2$ requires 314.9894 and $C_{15}H_{10}{}^{81}BrNO_2$ requires 316.9874; $R_f$ (*n*-hexanes/ethyl acetate: 8/1): 0.14; mp : 168°C (lit. 157-162°C)[207]

**4-Aminobenzyl alcohol (185)**

A solution of 4-nitrobenzyl alcohol (4.54 g, 30 mmol) and palladium (10 wt. % on activated carbon) (1.03 g, 10 mmol) in ethanol (50 mL) was stirred overnight at room temperature under a hydrogen atmosphere. The reaction mixture was then filtered through a short column of celite and the filtrate concentrated under vacuum. Purification by column chromatography, eluting first with DCM, then with DCM/MeOH/$NH_4OH$: 300/10/1, gave two main fractions, one containing *p*-toluidine (0.54 g, 17 %) and the other containing the desired product **185** as a light-brown solid (2.46 g, 67 %).

$^1$H NMR (270 MHz, $CDCl_3$): 1.65 (br, s, 1H, N*H*H or OH), 2.15 (br, s, 1H, N*H*H or OH), 3.66 (br, s, 1H, NH*H*), 4.50 (s, 2H, $CH_2$), 6.64 (d, 2H, *J*=8.4 Hz), 7.12 (d, 2H, *J*=8.4 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 65.05 ($CH_2$), 115.09 (CH), 128.67 (CH), 131.04 (C), 145.86 (C); MS (FAB): *m/z* = 123 (M); $C_7H_9NO$ requires 123

**Side product: *p*-toluidine**

$^1$H NMR (270 MHz, $CDCl_3$): 2.30 (s, 3H, $CH_3$), 3.58 (br, s, 2H, $NH_2$), 6.63 (d, 2H, *J*=8.1 Hz), 7.02 (d, 2H, *J*=8.1 Hz); $^{13}$ C NMR (67.8 MHz, $CDCl_3$): 21.12 ($CH_3$), 115.37 (CH), 128.52 (C), 129.88 (CH), 145.12 (C); MS (EI): *m/z* = 165.0790 (M); $C_7H_9N$ requires 165.0789; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.65

**4-Amino-*O*-(tetrahydropyranyl)benzyl alcohol (189)** [208]

A solution of 4-nitrobenzyl alcohol (1.53 g, 10.00 mmol), 3,4-dihydro-2*H*-pyran (0.84 g, 0.91 mL, 10.00 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.11 mmol) was stirred overnight at room temperature in $CHCl_3$, then washed several times with water and brine, dried ($MgSO_4$) and finally concentrated under vacuum. Purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 9/1, afforded **188** (2.06 g, 87 %). Palladium (10 wt. % on activated carbon) (0.29 g, 0.27 mmol) was added to a solution of **188** (2.00 g, 8.43 mmol) in ethanol (20 mL). The reaction mixture was stirred overnight at room temperature under a hydrogen atmosphere and then filtered through a short column of celite. The solvent was evaporated and the crude product purified by column chromatography, eluting with *n*-hexanes/ethyl acetate: 5/1, which gave **189** as an orange oil (0.80 g, 46 %).

IR $\nu_{max}$/cm (neat): 3446, 3360 (br, bonded NH), 1625 (N-H); $^1$H NMR (270 MHz, $CDCl_3$): 1.42-1.89 (m, 6H), 3.47-3.55 (m, 1H), 3.68 (br, s, 2H, $NH_2$), 3.86-3.95 (m, 1H), 4.36 (d, 1H, *J*=11.3 Hz, C*H*HO), 4.64 (d, 1H, *J*=11.3 Hz, CH*H*O), 4.64-4.67 (m, 1H, OCHO), 6.60 (d, 2H, *J*=8.4 Hz), 7.12 (d, 2H, *J*=8.4 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 19.02 ($CH_2$), 25.06 ($CH_2$), 30.18 ($CH_2$), 61.59 ($CH_2$), 68.29 ($CH_2$Ph), 96.78 (CH), 114.29 (CH), 126.98 (C), 129.10 (CH), 145.97 (C); MS (FAB): *m/z* = 207.1266 (M) and 208.1337 (M+H); $C_{12}H_{18}NO_2$ requires 208.1337; $R_f$ (*n*-hexanes/ethyl acetate: 8/1): 0.66

**4-Phthalimido-*O*-(tetrahydropyranyl)benzyl alcohol (190)**

A solution of **189** (0.40 g, 1.93 mmol) and phthalic anhydride (0.28 g, 1.93 mmol) in mixed xylenes (6 mL) was reacted according to the general procedure H, giving **190** (0.10 g, 16 %) as a white solid.

IR $\nu_{max}$/cm (neat): 1707 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 1.47-1.91 (m, 6H), 3.50-3.59 (m, 1H), 3.86-3.95 (m, 1H), 4.54 (d, 1H, *J*=12.5 Hz, C*H*HO), 4.72 (t, 1H, *J*=3.2 Hz, OCHO), 4.81 (d, 1H, *J*=12.5 Hz, CH*H*O), 7.42 (d, 2H, *J*=8.6 Hz), 7.48 (d, 2H, *J*=8.6 Hz), 7.73-7.79 (m, 2H), 7.90-7.96 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 19.21 ($CH_2$), 25.38 ($CH_2$), 30.45 ($CH_2$), 62.02 ($CH_2$), 68.04 ($CH_2$Ph), 97.62 (CH), 123.69 (CH), 126.43 (CH), 128.30 (CH), 130.75 (C), 131.70 (C), 134.34 (CH), 138.36 (C), 167.24 (CO); MS (FAB): *m/z* = 337.1315 (M) and 338.1396 (M+H);

$C_{20}H_{20}NO_4$ requires 338.1382; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.12, $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.64; mp : 125°C

**4-Amino-*O*-(*tert*-butyldimethylsilyl)benzyl alcohol (191)** [209,210]

4-Aminobenzyl alcohol (1.17 g, 9.5 mmol), *tert*-butyldimethylsilyl chloride (2.15 g, 14.2 mmol) and imidazole (1.29 g, 19.0 mmol) were reacted according to the general procedure G. After purification by column chromatography, eluting with *n*-hexanes/ethyl acetate: 8/1, **191** was isolated as an orange oil (1.82 g, 81 %).

IR $\nu_{max}$/cm (neat): 3445, 3363 (br, bonded NH), 1622 (N-H); $^1$H NMR (270 MHz, $CDCl_3$): 0.13 (s, 6H, 2x$CH_3$), 0.97 (s, 9H, C($CH_3$)$_3$), 3.62 (s, br, $NH_2$), 4.66 (s, 2H, $CH_2$), 6.66 (d, 2H, *J*=8.0 Hz), 7.14 (d, 2H, *J*=8.0 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): -5.22 (2x$CH_3$), 18.34 (*C*($CH_3$)$_3$), 25.91 (C(*C*$H_3$)$_3$), 64.91 ($CH_2$), 114.83 (CH), 127.57 (CH), 131.28 (C), 145.33 (C); MS (FAB): *m/z* = 237.1555 (M), 238.1614 (M+H); $C_{13}H_{24}NOSi$ requires 238.1626; $R_f$ (*n*-hexanes/ethyl acetate: 8/1): 0.17, $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.73

**3-Amino-*O*-(*tert*-butyldimethylsilyl)benzyl alcohol (192)** [210,211]

3-Aminobenzyl alcohol (1.85 g, 15 mmol), *tert*-butyldimethylsilyl chloride (3.39 g, 22.5 mmol) and imidazole (2.04 g, 30 mmol) were reacted according to the general procedure G. **192** was isolated as a dark oil (2.89 g, 81 %).

IR $\nu_{max}$/cm (neat): 3449, 3361 (br, bonded NH), 1620 (N-H); $^1$H NMR (270 MHz, $CDCl_3$): 0.12 (s, 6H, 2x$CH_3$), 0.97 (s, 9H, C($CH_3$)$_3$), 3.65 (br, 2H, $NH_2$), 4.68 (s, 2H, $CH_2$), 6.65-6.60 (m, 1H), 6.67-6.75 (m, 2H), 7.12 (t, 1H, *J*=7.7 Hz), 7.89-7.95 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): -5.31 (2x$CH_3$), 18.37 (*C*($CH_3$)$_3$), 25.91 (C(*C*$H_3$)$_3$), 64.83 ($CH_2$), 112.67 (CH), 113.61 (CH), 116.17 (CH), 129.01 (CH), 142.61 (C), 146.30 (C); MS (FAB): *m/z* = 237.1537 (M), 238.1622 (M+H); $C_{13}H_{24}NOSi$ requires 238.1626; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.38, $R_f$ (*n*-hexanes/ethyl acetate: 1/1): 0.54

**2-Amino-*O*-(*tert*-butyldimethylsilyl)benzyl alcohol (193)** [212]

2-Aminobenzyl alcohol (1.23 g, 10 mmol), *tert*-butyldimethylsilyl chloride (2.26 g, 15 mmol) and imidazole (1.36 g, 20 mmol) were reacted according to the general procedure G. **193** was isolated as a brown oil (2.32 g, 98 %).

IR $\nu_{max}$/cm (neat): 3461, 3373 (br, bonded NH), 1621 (N-H); $^1$H NMR (270 MHz, $CDCl_3$): 0.08 (s, 6H, 2x$CH_3$), 0.91 (s, 9H, C($CH_3$)$_3$), 4.69 (s, 2H, $CH_2$), 6.65-6.75 (m, 2H), 7.02-7.15 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): -5.29 (2x$CH_3$), 18.17 (*C*($CH_3$)$_3$), 25.84 (C(*C*$H_3$)$_3$), 64.84 ($CH_2$), 115.64 (CH), 117.80 (CH), 125.13 (C), 128.39 (CH), 128.65 (CH), 146.06 (C); MS (FAB): *m/z* = 237.1551 (M), 238.1607 (M+H); $C_{13}H_{24}NOSi$ requires 238.1626; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.65

**4-Phthalimido-*O*-(*tert*-butyldimethylsilyl)benzyl alcohol (194)**

A solution of **191** (3.96 g, 16.7 mmol) and phthalic anhydride (2.42 g, 16.3 mmol) in mixed xylenes (40 mL) was reacted according to the general procedure H, which afforded **194** as colourless crystals (2.72 g, 45%).

IR $\nu_{max}$/cm (neat): 2942-2857 (C-H aromatic), 1714 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 0.09 (s, 6H, 2x$CH_3$), 0.94 (s, 9H, C($CH_3$)$_3$), 4.79 (s, 2H, $CH_2$), 7.39 (d, 2H, *J*=8.5 Hz), 7.45 (d, 2H, *J*=8.5 Hz), 7.72-7.79 (m, 2H), 7.89-7.95 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): -5.37 (2x$CH_3$), 18.27 (*C*($CH_3$)$_3$), 25.82 (C(*C*$H_3$)$_3$), 64.28 ($CH_2$), 123.53 (CH), 126.21 (CH), 126.39 (CH), 130.12 (C), 131.62 (C), 134.20 (CH), 141.35 (C), 167.16 (CO); MS (FAB): 368.1673; $C_{21}H_{26}NO_3Si$ requires 368.1681; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.41; mp : 114°C

**3-Phthalimido-*O*-(*tert*-butyldimethylsilyl)benzyl alcohol (195)**

A solution of **192** (1.29 g, 5.43 mmol) and phthalic anhydride (0.77 g, 5.43 mmol) in mixed xylenes (30 mL) was reacted according to the general procedure H. **195** was isolated as a white solid (1.33 g, 71 %).

IR $\nu_{max}$/cm (neat): 1721 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 0.10 (s, 6H, 2x$CH_3$), 0.93 (s, 9H, C($CH_3$)$_3$), 4.79 (s, 2H, $CH_2$), 7.24-7.52 (m, 4H), 7.76-7.79 (m, 2H), 7.93-7.96 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): -5.45 (2x$CH_3$), 18.17 (*C*($CH_3$)$_3$), 25.75

($C(CH_3)_3$), 64.22 ($CH_2$), 123.40 (CH), 123.84 (CH), 124.76 (CH), 125.34 (CH), 128.67 (CH), 131.42 (C), 131.47 (C), 134.11 (CH), 142.47 (C), 166.93 (CO); MS (FAB): *m/z* = 367.1572 (M) and 368.1672 (M+H); $C_{21}H_{25}NO_3Si$ requires 367.1603; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.42; mp : 87°C

**2-Phthalimido-*O*-(*tert*-butyldimethylsilyl)benzyl alcohol (196)**

A solution of **193** (0.20 g, 0.84 mmol) and phthalic anhydride (0.12 g, 0.84 mmol) in mixed xylenes (5 mL) was reacted according to the general procedure H. **196** was isolated as a white solid (0.28 g, 96 %).

IR $\nu_{max}$/cm (neat): 1716 (CO); $^1$H NMR (270 MHz, $CDCl_3$): -0.06 (s, 6H, 2x$CH_3$), 0.79 (s, 9H, $C(CH_3)_3$), 4.65 (s, 2H, $CH_2$), 7.22 (dd, 1H, *J*=1.3 and 7.5 Hz), 7.39 (virtual double triplet, 1H, *J*=1.7 and 7.4 Hz), 7.46 (virtual double triplet, 1H, *J*=1.5 and 7.4 Hz), 7.58 (dd, 1H, *J*=1.4 and 7.3 Hz), 7.75-7.79 (m, 2H), 7.92-7.96 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): -5.60 (2x$CH_3$), 18.17 ($C(CH_3)_3$), 25.69 ($C(CH_3)_3$), 62.39 ($CH_2$), 123.66 (CH), 127.91 (CH), 128.12 (CH), 128.89 (CH), 129.07 (C), 129.28 (CH), 132.06 (C), 134.20 (CH), 139.15 (C), 167.18 (CO); MS (FAB): 368 (M+H); $C_{21}H_{25}NO_3Si$ requires 367; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.42; mp : 122-123°C

**17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-tetraacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(4-phthalimidobenzylimino)[7,7'-bimorphinan] (197)**

**178** (0.34 g, 0.41 mmol), sodium hydride (60% in oil, 66 mg, 1.65 mmol), 18-crown-6 (23 mg, 0.09 mmol) and **182** (0.38 g, 1.20 mmol) in dry THF (5 mL) were reacted according to general procedure I. After purification, **197** was obtained as a brown solid (0.23 g, 53%).

$^1$H NMR (270 MHz, $CDCl_3$): 0.04 (d, 4H, *J*=4.5 Hz, $NCH_2CH(CHHCHH)$), 0.43 (d, 4H, *J*=8.0 Hz, $NCH_2CH(CHHCHH)$), 0.66-0.78 (m, 2H, $NCH_2CH(CH_2CH_2)$), 1.56 (d, 2H, *J*=10.9 Hz), 1.90 (s, $CH_3$), 2.05 ($CH_3$), 4.44 (d, 2H, *J*=5.9 Hz), 5.29 (s, 2H, 5-H + 5'-H), 5.32 (d, 1H, *J*=16.8 Hz, NCHHPh), 5.44 (d, 1H, *J*=16.8 Hz, NCHHPh), 6.62 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.75 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 6.87 (d, 2H, *J*=8.4 Hz), 7.34 (d, 2H, *J*=8.4 Hz), 7.75-7.79 (m, 2H), 7.89-7.92 (m, 2H); $^{13}$C NMR

(100.5 MHz, $CDCl_3$): 4.05 (2x$NCH_2CH(CH_2CH_2)$), 4.40 (2x$NCH_2CH(CH_2CH_2)$), 10.07 (2x$NCH_2CH(CH_2CH_2)$), 21.00 (2x$CH_3$), 23.02 (2x$CH_3$), 24.36 (10-C + 10'-C), 25.19 (8-C + 8'-C), 31.55 (15-C + 15'-C), 43.85 (16-C + 16'-C), 47.71 ($CH_2$), 48.59 (13-C + 13'-C), 56.33 (9-C + 9'-C), 59.94 (18-C + 18'-C), 84.22 (14-C + 14'-C), 85.45 (5-C + 5'-C), 116.21, 118.70 (CH), 122.28 (CH), 123.87 (CH), 125.93 (C), 126.54 (CH), 126.77 (CH), 130.63 (C), 131.28 (C), 131.88 (C), 132.14 (C), 132.86 (C), 134.61 (CH), 139.12 (C), 147.15 (C), 167.29 (CO), 168.88 (CO), 170.86 (CO)

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(4-phthalimidobenzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (204)**

**197** (0.20 g, 0.19 mmol) was dissolved in conc. HCl/methanol (3 mL, 1/1) and the solution was stirred for 72 hours at 80°C. The solvents were then removed by evaporation, water was added and the aqueous phase basified to pH=8 ($NH_4OH$) and extracted with DCM/MeOH: 5/1. The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The crude material was purified by column chromatography, eluting first with $CHCl_3$/MeOH/$NH_4OH$: 500/10/1 then with $CHCl_3$/MeOH/$NH_4OH$: 250/10/1. **204** was isolated as an off-white solid (9 mg, 5%).

$^1H$ NMR (270 MHz, $CDCl_3$): 0.11 (d, 4H, *J*=4.4 Hz, $NCH_2CH(CHHCHH)$), 0.51 (d, 4H, *J*=7.7 Hz, $NCH_2CH(CHHCHH)$), 0.78-0.89 (m, 2H, $NCH_2CH(CH_2CH_2)$), 1.59 (d, 2H, *J*=9.7 Hz), 3.02 (d, 2H, *J*=18.3 Hz), 3.17-3.25 (m, 2H), 5.31 (d, 1H, *J*=17.8 Hz, NCHHPh), 5.36 (s, 2H, 5-H + 5'-H), 5.55 (d, 1H, *J*=17.8 Hz, NCHHPh), 6.47 (d, 2H, *J*=8.3 Hz, 1-H + 1'-H), 6.59 (d, 2H, *J*=8.3 Hz, 2-H + 2'-H), 6.94 (d, 2H, *J*=8.2 Hz), 7.30 (d, 2H, *J*=8.2 Hz), 7.77-7.80 (m, 2H), 7.93-7.96 (m, 2H); MS (FAB): *m/z* = 897 (M); $C_{55}H_{52}N_4O_8$ requires 897; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.44; mp > 200°C

**4-(Phthalimidomethyl)benzyl bromide (206)**

A mixture of dibromo-*p*-xylene (1.0 g, 3.8 mmol), potassium phthalimide (0.7 g, 3.8 mmol) and 18-crown-6 (0.1 g, 0.4 mmol) in toluene (10 mL) was reacted according to the general procedure J. **206** was isolated as a white solid (0.60 g, 48 %).

IR $\nu_{max}$/cm (KBr): 3049-2938 (C-H aromatic), 1720 (CO); $^1$H NMR (270 MHz, $CDCl_3$ : 4.42 (s, 2H, $CH_2Br$), 4.81 (s, 2H, $CH_2N$), 7.31 (d, 2H, *J*=8.2 Hz), 7.39 (d, 2H, *J*=8.2 Hz), 7.67-7.70 (m, 2H), 7.81-7.84 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 32.96 ($CH_2Br$), 41.09 ($CH_2N$), 123.28 (CH), 128.99 (CH), 129.28 (CH), 131.94 (C), 133.96 (CH), 136.51 (C), 137.29 (C), 167.83 (CO); MS (FAB): *m/z* = 330.0125 (M+H, $^{79}$Br) and 332.0125 (M+H, $^{81}$Br); $C_{16}H_{13}{}^{79}BrNO_2$ requires 330.0129 and $C_{16}H_{13}{}^{81}BrNO_2$ requires 332.0108; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.23; mp : 137°C

**3-(Phthalimidomethyl)benzyl bromide (207)**

A mixture of dibromo-*m*-xylene (2.0 g, 7.6 mmol), potassium phthalimide (1.4 g, 7.6 mmol) and 18-crown-6 (0.20 g, 0.76 mmol) in toluene (20 mL) was reacted according to the general procedure J, affording **207** as colourless crystals (1.35 g, 54%).

IR $\nu_{max}$/cm (KBr): 3042-2931 (C-H aromatic), 1709 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 4.44 (s, 2H, $CH_2Br$), 4.82 (s, 2H, $CH_2N$), 7.27-7.38 (m, 3H), 7.44 (s, 1H), 7.67-7.71 (m, 2H), 7.80-7.85 (m, 2H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 33.54 ($CH_2Br$), 41.71 ($CH_2N$), 123.62 (CH), 128.83 (CH), 128.94 (CH), 129.38 (CH), 129.40 (CH), 132.22 (C), 134.23 (CH), 137.09 (C), 138.42 (C), 168.08 (CO); MS (FAB): *m/z* = 330.0118 (M+H, $^{79}$Br ) and 332.0127 (M+H, $^{81}$Br); $C_{16}H_{13}{}^{79}BrNO_2$ requires 330.0129 and $C_{16}H_{13}{}^{81}BrNO_2$ requires 332.0108; $R_f$ (*n*-hexanes/ethyl acetate: 4/1 ): 0.24; mp : 124°C

**2-(Phthalimidomethyl)benzyl bromide (208)** [213]

A mixture of dibromo-*o*-xylene (3.0 g, 11.3 mmol), potassium phthalimide (2.1 g, 11.3 mmol) and 18-crown-6 (0.30 g, 1.13 mmol) in toluene (30 mL) was reacted according to the general procedure J. **208** was isolated as a white solid (1.77 g, 47 %).

IR $\nu_{max}$/cm (KBr): 1712 (CO); $^1$H NMR (400 MHz, $CDCl_3$): 4.82 (s, 2H, $CH_2Br$), 4.97 (s, 2H, $CH_2N$), 7.21-7.27 (m, 2H), 7.31-7.39 (m, 1H), 7.42-7.45 (m, 1H), 7.68-7.70 (m, 2H), 7.81-7.84 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 31.38 ($CH_2Br$), 38.18 ($CH_2N$), 123.29 (CH), 128.38 (CH), 129.13 (CH), 130.34 (CH), 130.57 (CH), 131.90 (C), 134.02 (CH), 134.84 (C), 136.02 (C), 168.03 (CO); MS (FAB): *m/z* = 330.0110

(M+H, $^{79}Br$) and 332.0120 (M+H, $^{81}Br$); $C_{16}H_{13}{}^{79}BrNO_2$ requires 330.0129 and $C_{16}H_{13}{}^{81}BrNO_2$ requires 332.0108; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.25; mp : 144°C

**17,17'-Bis(cyclopropylmethyl)-3,3'-(methoxymethyloxy)-14,14'-dimethoxy 6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(methoxymethylimino)[7,7'-bimorphinan] (209)**

To a solution of norBNI **(13)** (0.33 g, 0.50 mmol) and imidazole (0.27 g, 4.0 mmol) in dry DMF (5 mL) was added trimethylsilyl chloride (0.38 mL, 3.0 mmol). The reaction mixture was stirred for two hours at room temperature, after which water (3 mL) was added and the aqueous phase extracted with DCM/MeOH: 5/1. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated under vacuum. **209** was isolated as a brown solid and used without any further purification (0.45 g, 95%).

IR $\nu_{max}$/cm (neat): no specific peak; $^1H$ NMR (270 MHz, $CDCl_3$): -0.23 (s, 18H, 6x$CH_3$), 0.08 (s, 18H, 6x$CH_3$), 0.03-0.18 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.44-0.54 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.78-0.94 (m, 2H, 2x$NCH_2CH(CH_2CH_2)$), 5.24 (s, 2H, 5-H + 5'-H), 6.41 (d, 2H, *J*=8.0 Hz, 1-H + 1'-H), 6.50 (d, 2H, *J*=8.0 Hz, 2-H + 2'-H)

**17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-(*tert*-butyldimethylsilyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (210)**

To a solution of norBNI **(13)** (0.66 g, 1.0 mmol) and imidazole (0.30 g, 4.4 mmol) in dry DMF (5 mL) was added *tert*-butyldimethylsilyl chloride (0.63 g, 4.2 mmol). The reaction mixture was stirred for two hours at room temperature, after which water (3 mL) was added and the aqueous phase extracted with DCM/MeOH: 5/1. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated under vacuum. **210** was isolated as a brown solid and used without any further purification (1.08 g, 97%).

IR $\nu_{max}$/cm (neat): no specific peak; $^1H$ NMR (270 MHz, $CDCl_3$): 0.01-0.10 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.08 (s, 12H, 3-$COSi(CH_3)_2$ + 3'-$COSi(CH_3)_2$), 0.09 (s, 6H, 14-$COSi(CH_3CH_3)$ + 14'-$COSi(CH_3CH_3)$), 0.10 (s, 6H, 14-$COSi(CH_3CH_3)$ + 14'-$COSi(CH_3CH_3)$), 0.49 (d, 4H, *J*=8.2 Hz, 2x$NCH_2CH(CHHCHH)$), 0.90 (s, 18H, 6x$CH_3$), 0.94 (s, 18H, 6x$CH_3$), 5.36 (s, 2H, 5-H + 5'-H), 6.43 (d, 2H, *J*=8.1 Hz, 1-H +

1'-H), 6.53 (d, 2H, *J*=8.1 Hz, 2-H + 2'-H), 7.94 (s, br, 1H, NH); $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.42

**17,17'-Bis(cyclopropylmethyl)-14,14'-dimethoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-3,3'-diol (211)** [163]

A solution of **221** (63 mg, 86 µmol) in conc. HCl/MeOH (3 mL, 1/1) was stirred overnight at 80°C. Similar workup and purification as employed for the preparation of **204** afforded **211** (47 mg, 79%) as an off-white solid.

$^1H$ NMR (270 MHz, $CDCl_3$): 0.12 (d, 4H, *J*=4.0 Hz, 2x$NCH_2CH(CHHCHH)$), 0.41-0.53 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.78-0.90 (m, 2H, 2x$NCH_2CH(CH_2CH_2)$), 3.09 (s, 6H, $OCH_3$), 5.55 (s, 2H, 5-H + 5'-H), 6.46 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.61 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H); $^{13}C$ NMR (100.5 MHz, $CDCl_3$): 3.08 (2x$NCH_2CH(CH_2CH_2)$), 4.30 (2x$NCH_2CH(CH_2CH_2)$), 8.76 (2x$NCH_2CH(CH_2CH_2)$), 22.28 ($CH_2$), 23.23 ($CH_2$), 29.82 (15-C + 15'-C), 44.88 (16-C + 16'-C), 48.10 ($CH_3$ or 13-C + 13'-C), 48.68 ($CH_3$ or 13-C + 13'-C), 55.32 (9-C + 9'-C), 59.24 (18-C + 18'-C), 78.79 (14-C + 14'-C), 85.31 (5-C + 5'-C), 114.92 (7-C + 7'-C), 117.15 (CH), 118.53 (CH), 124.81 (C), 124.97 (C), 130.81 (C), 139.19 (C), 142.63 (C); $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.39; mp > 215°C

**4,5α-Epoxy-3-benzyloxy-14-methoxy-17-cyclopropylmethyl-morphinan-6-one (212)** [164]

A mixture of **215** (6.97 g, 16.2 mmol) and sodium hydride (1.94 g, 48.5 mmol) in dry DMF (20 mL) was stirred for 20 minutes at 0°C. Dimethyl sulfate (4.21 mL, 44.5 mmol) was then added dropwise. After complete addition, the temperature was maintained at 0°C for another 2 hours before quenching the reaction with water (5 mL). The aqueous phase was extracted with DCM/MeOH: 5/1, the organic phase dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography, eluting first with $CHCl_3$: 100%, then with $CHCl_3$/MeOH/$NH_4OH$: 400/5/1. The product was immediately dissolved in MeOH/conc. HCl: 3/2, and the solution was refluxed overnight. The solvents were then removed under vacuum, and recrystallisation in ethanol afforded **212** (HCl salt) as a white solid (4.15 g, 72%).

IR $\nu_{max}$/cm (KBr, HCl salt): 3391 (br, bonded OH), 1730 (CO); $^1$H NMR (270 MHz, $CDCl_3$, free base): 0.13 (d, 2H, *J*=5.3 Hz, $NCH_2CH(CHHCHH)$), 0.44-0.57 (m, 2H, $NCH_2CH(CHHCHH)$), 0.81-0.95 (m, 1H, $NCH_2CH(CH_2CH_2)$), 3.11 (d, 1H, *J*=18.3 Hz, 10-C*H*H), 3.37 (s, 3H, $OCH_3$), 3.63 (d, 1H, *J*=5.3 Hz, 9-C*H*H), 4.65 (s, 1H, 5-H), 6.55 (d, 1H, *J*=8.2 Hz, 1-H), 6.69 (d, 1H, *J*=8.2 Hz, 2-H); $^{13}$C NMR (67.8 MHz, $CDCl_3$, free base): 3.16 ($NCH_2CH(CH_2CH_2)$), 4.29 ($NCH_2CH(CH_2CH_2)$), 9.12 ($NCH_2CH(CH_2CH_2)$), 22.63 (10-C), 25.04 (8-C), 29.15 (15-C), 35.46 (7-C), 44.88 (16-C), 47.98 ($OCH_3$), 51.02 (13-C), 54.43 (9-C), 59.24 (18-C), 75.59 (14-C), 90.49 (5-C), 117.85 (2-C), 119.81 (1-C), 124.94 (11-C), 129.42 (12-C), 138.76 (3-C), 143.45 (4-C), 210.28 (CO); MS (FAB, free base): *m/z* = 355.1771 (M), 356.1850 (M+H); $C_{21}H_{26}NO_4$ requires 356.1861; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1, free base): 0.45; mp (HCl salt) > 220 °C

**4,5α-Epoxy-3-benzyloxy-17-cyclopropylmethyl-morphinan-6-one (215)** [164]

To a solution of naltrexone (5.80 g, 17.01 mmol) and potassium carbonate (3.52 g, 22.47 mmol) in DMF (20 mL) was added benzyl bromide (2.04 mL, 17.1 mmol). The reaction mixture was stirred overnight at room temperature. Water (7 mL) was added, the aqueous phase extracted with DCM/MeOH: 5/1 and the organic phase was dried ($MgSO_4$) and concentrated. **215** was isolated as a brown solid (7.26 g, 99%) and used with no further purification.

$^1$H NMR (270 MHz, $CDCl_3$): 0.10-0.15 (m, 2H, $NCH_2CH(CHHCHH)$), 0.51-0.57 (m, 2H, $NCH_2CH(CHHCHH)$), 0.78-0.91 (m, 1H, $NCH_2CH(CH_2CH_2)$), 5.19 (d, 1H, *J*=12.3 Hz, OC*H*H), 5.27 (d, 1H, *J*=12.3 Hz, OCH*H*), 5.28 (s, 1H, 5-H), 6.54 (d, 1H, *J*=8.1 Hz, 1-H), 6.70 (d, 1H, *J*=8.1 Hz, 2-H), 7.26-7.36 (m, 3H, Ar), 7.41-7.46 (m, 2H, Ar); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.77 ($NCH_2CH(CH_2CH_2)$), 3.96 ($NCH_2CH(CH_2CH_2)$), 9.38 ($NCH_2CH(CH_2CH_2)$), 22.63 (10-C), 30.68 ($CH_2$), 31.45 ($CH_2$), 36.18 (7-C), 43.53 (16-C), 50.71 (13-C), 59.16 (18-C), 61.96 (9-C), 70.10 (14-C), 72.04 ($OCH_2$), 90.38 (5-C), 117.87 (CH), 119.37 (CH), 125.55 (C), 127.72 (CH), 128.34 (CH), 129.76 (C), 137.41 (C), 141.74 (C), 145.46 (C), 162.47 (CH), 208.49 (CO); MS (FAB): *m/z* = 431.2093 (M), 432.2171 (M+H); $C_{27}H_{30}NO_4$ requires 432.2174

**4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one (217)** [214]

Method A.

A solution of hydrocodone (4.00 g, 13.4 mmol) in DCM (80 mL) was cooled to -78°C under a nitrogen atmosphere before adding slowly boron tribromide (1 mol/L in DCM, 26.6 mL, 26.6 mmol). The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was then quenched by the addition of methanol (50 mL) and the solvents were removed under vacuum. Methanol (50 mL) was added a second time and removed by evaporation. Water (50 mL) was added and the pH adjusted to pH=12 ($NH_4OH$). The aqueous phase was extracted several times with DCM/MeOH: 5/1. The organic phase was dried over $MgSO_4$, concentrated under vacuum and the brown oil was purified by column chromatography, eluting with $CHCl_3$/MeOH/$NH_4OH$: 500/10/1. **217** was obtained as a brown solid (1.50 g, 40%).

Method B.

A solution of hydrocodone (2.10 g, 7.0 mmol) in dichloroethane (10 mL) was added slowly to a solution of boron tribromide-methyl sulfide complex (8.74 g, 28.0 mmol) in dichloroethane (40 mL). The reaction mixture was stirred overnight at 65°C. Similar workup and purification as employed for method A afforded **217** as a brown solid (0.66 g, 33 %).

IR $\nu_{max}$/cm (neat): 3380 (br, bonded OH), 1724 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 2.44 (NMe), 4.59 (5-H), 6.53 (d, 1H, *J*=8.1 Hz, 1-H), 6.64 (d, 1H, *J*=8.1 Hz, 2-H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 19.94 (10-C), 25.21 (8-C), 34.61 (15-C), 40.00 (7-C), 41.27 (14-C), 42.17 (N-Me), 46.50 (13-C), 46.68 (16-C), 58.74 (9-C), 90.81 (5-C), 118.28 (CH), 119.87 (CH), 123.80 (C), 126.56 (C), 139.95 (C), 144.36 (C), 208.77 (CO); MS (FAB): *m/z* = 286.1431 (M+H); $C_{17}H_{20}NO_3$ requires 286.1442; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.30; mp > 220°C

**4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one (218)** [170,215]

Oxycodone (0.58 g, 1.84 mmol) in dichloroethane (10 mL) was added slowly to a solution of boron tribromide-methyl sulfide complex (2.29 g, 7.33 mmol) in dichloroethane (20 mL). The reaction mixture was stirred overnight at 65°C, water was then added, before stirring for another 30 minutes. The aqueous phase was

washed several times with DCM, adjusted to pH=12 with diluted $NH_4OH$ and extracted several times with DCM/MeOH: 5/1. The organic phase was dried over $MgSO_4$, concentrated under vacuum and the brown oil was purified by column chromatography, eluting with $CHCl_3$/MeOH/$NH_4OH$: 220/10/1. **218** was obtained as a brown solid (0.35 g, 63 %).

$^1$H NMR (270 MHz, $CDCl_3$): 2.39 (s, 3H, $CH_3$), 2.88 (d, 1H, *J*=5.7 Hz), 3.02 (td, 1H, *J*=14.6 Hz and 5.2 Hz), 3.12 (d, 1H, *J*=18.6 Hz), 4.70 (s, 1H, 5-H), 6.58 (d, 1H, *J*=8.2 Hz, 1-H), 6.70 (d, 1H, *J*=8.2 Hz, 2-H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 21.99 (10-C), 30.39 ($CH_2$), 31.30 ($CH_2$), 36.15 (7-C), 42.76 (N-Me), 45.28 (16-C), 50.46 (13-C), 64.56 (9-C), 70.60 (14-C), 90.51 (5-C), 118.15 (CH), 120.00 (CH), 124.12 (C), 128.85 (C), 138.97 (C), 143.57 (C), 210.21 (CO); $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.47; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-3,3'-(methoxymethyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(methoxymethylimino)[7,7'-bimorphinan]-14,14'-diol (219)**
A mixture of norBNI **(13)** (0.80 g, 1.20 mmol) and sodium hydride (192 mg, 4.80 mmol) in dry DMF (10 mL) was stirred for 20 minutes at room temperature before adding chloromethyl methyl ether (0.36 mL, 4.80 mmol) and stirring continued for a further 2 hrs at room temperature. Water (4 mL) was added and the aqueous phase extracted with DCM/MeOH: 5/1. The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The product was purified by column chromatography, eluting first with $CHCl_3$: 100%, then with $CHCl_3$/MeOH/$NH_4OH$: 800/5/1, which afforded **219** as a brown solid (0.72 g, 76%).

IR $\nu_{max}$/cm (KBr): 3295 (br, bonded OH); $^1$H NMR (270 MHz, $CDCl_3$): 0.10 (d, 4H, *J*=4.2 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.50 (d, 4H, *J*=6.9 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.75-0.87 (m, 2H, 2xNCH$_2$C*H*($CH_2CH_2$)), 3.37 (s, 3H, NCH$_2$OC*H*$_3$), 3.44 (s, 6H, 2xOCH$_2$OC*H*$_3$), 5.06 (d, 2H, *J*=6.5 Hz, OC*H*HOCH$_3$), 5.16 (d, 2H, *J*=6.5 Hz, OCH*H*OCH$_3$), 5.19 (d, 1H, *J*=10.3 Hz, NC*H*HOCH$_3$), 5.62 (s, 2H, 5-H + 5'-H), 5.78 (d, 1H, *J*=10.3 Hz, NCH*H*OCH$_3$), 6.50 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.82 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.67 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.85 (2xNCH$_2$CH(CH$_2$*C*H$_2$)), 9.29 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 22.93 (2x$CH_2$), 28.76

(2x$CH_2$), 31.42 (2x$CH_2$), 43.50 (16-C + 16'-C), 47.61 (13-C + 13'-C), 55.51 ($NCH_2OCH_3$), 56.09 (3-$COCH_2OCH_3$ + 3'-$COCH_2OCH_3$), 59.21 (18-C + 18'-C), 62.14 (9-C + 9'-C), 72.35 (14-C + 14'-C), 75.02 ($NCH_2OCH_3$), 84.22 (5-C + 5'-C), 95.66 (3-$COCH_2OCH_3$ + 3'-$COCH_2OCH_3$), 116.60 (C), 117.67 (CH), 118.19 (CH), 125.89 (C), 126.99 (C), 131.21 (C), 140.35 (C), 145.25 (C); $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.54; mp : 114 °C

**17,17'-Bis(cyclopropylmethyl)-3,3'-(methoxymethyloxy)-14,14'-dimethoxy-6,6', 7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(methoxymethylimino)[7,7'-bimorphinan] (220)**

**219** (0.65 g, 0.83 mmol), sodium hydride (0.10 g, 2.50 mmol) and dimethyl sulfate (0.2 mL, 2.1 mmol) were reacted according to the same procedure as used for the preparation of **212**, but the reaction time was increased to 3hrs. After purification by column chromatography, eluting first with $CHCl_3$: 100%, then with $CHCl_3$/MeOH/$NH_4OH$: 400/5/1, **220** was isolated as a brown solid (0.15 g, 22%).

IR $\nu_{max}$/cm (neat): 2913 (C-H aromatic); $^1$H NMR (270 MHz, $CDCl_3$): 0.11 (d, 4H, *J*=4.2 Hz, 2x$NCH_2CH(CHHCHH)$), 0.46-0.51 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.82-0.92 (m, 2H, 2x$NCH_2CH(CH_2CH_2)$), 3.13 (s, 6H, 14-$OCH_3$ + 14'-$OCH_3$), 3.33 (s, 3H, $NCH_2OCH_3$), 3.43 (s, 6H, 2x$OCH_2OCH_3$), 5.08 (d, 2H, *J*=6.5 Hz, $OCHHOCH_3$), 5.16 (d, 1H, *J*=10.3 Hz, $NCHHOCH_3$), 5.18 (d, 2H, *J*=6.5 Hz, $OCHHOCH_3$), 5.59 (s, 2H, 5-H +5'-H), 5.72 (d, 1H, *J*=10.3 Hz, $NCHHOCH_3$), 6.52 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.82 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.01 (2x$NCH_2CH(CH_2CH_2)$), 4.20 (2x$NCH_2CH(CH_2CH_2)$), 9.03 (2x$NCH_2CH(CH_2CH_2)$), 22.17 (8-C + 8'-C), 23.09 (10-C + 10'-C), 29.99 (15-C + 15'-C), 44.77 (16-C + 16'-C), 48.12 (13-C + 13'-C), 48.53 (14-COCH3 + 14'-COCH3), 55.13 (9-C + 9'-C), 55.30 ($NCH_2OCH_3$), 56.18 (3-$OCH_2OCH_3$ + 3'-$OCH_2OCH_3$), 59.32 (18-C + 18'-C), 75.05 ($NCH_2OCH_3$), 77.99 (14-C + 14'-C), 84.44 (5-C + 5'-C), 95.68 (3-$OCH_2OCH_3$ + 3'-$OCH_2OCH_3$), 116.11 (7-C + 7'-C), 117.61 (2-C + 2'-C), 117.91 (1-C + 1'-C), 125.88 (6-C + 6'-C), 127.82 (11-C + 11'-C), 131.80 (12-C + 12'-C), 140.19 (3-C + 3'-C), 145.17 (4-C + 4'-C); MS (FAB): *m/z* = 821 (M), $C_{48}H_{59}N_3O_9$ requires 821; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.45; mp > 200°C

**17,17'-Bis(cyclopropylmethyl)-14,14'-dimethoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(methoxymethylimino)[7,7'-bimorphinan]-3,3'-diol (221)**

A solution of **220** (0.11 g, 0.13 mmol) in conc. HCl/MeOH (3 mL, 1/1) was stirred at room temperature overnight. The mixture was evaporated to dryness, water was added and the pH adjusted to pH=10 with diluted $NH_4OH$. The aqueous phase was extracted with DCM/MeOH: 5/1, the organic phase dried over $MgSO_4$ and concentrated by evaporation. Purification by column chromatography, eluting first with $CHCl_3$: 100%, then with $CHCl_3$/MeOH/$NH_4OH$: 500/10/1 and finally with $CHCl_3$/MeOH/$NH_4OH$: 250/10/1, afforded **221** (70 mg, 71%) as an off-white solid.

IR $\nu_{max}$/cm (neat): 3370 (br, bonded OH); $^1$H NMR (270 MHz, $CDCl_3$): 0.02-0.10 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.42-0.52 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.86-0.98 (m, 2H, 2x$NCH_2CH(CH_2CH_2)$), 2.56 (s, 6H, 14-$OCH_3$ + 14'-$OCH_3$), 3.30 (s, 3H, $NCH_2OCH_3$), 5.34 (d, 1H, *J*=9.7 Hz, $NCHHOCH_3$), 5.58 (s, 2H, 5-H +5'-H), 5.81 (d, 1H, *J*=9.7 Hz, $NCHHOCH_3$), 6.42 (d, 2H, *J*=7.8 Hz, 1-H + 1'-H), 6.53 (d, 2H, *J*=7.8 Hz, 2-H + 2'-H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.71 (2x$NCH_2CH(CH_2CH_2)$), 4.37 (2x$NCH_2CH(CH_2CH_2)$), 8.56 (2x$NCH_2CH(CH_2CH_2)$), 23.26 ($CH_2$), 24.49 ($CH_2$), 29.47 (15-C + 15'-C), 44.54 (16-C + 16'-C), 47.89 (13-C + 13'-C), 50.21 (14-COCH3 + 14'-COCH3), 55.18 ($OCH_3$), 58.69 (9-C + 9'-C), 59.88 (18-C + 18'-C), 70.56 ($NCH_2O$), 78.25 (14-C + 14'-C), 84.07 (5-C + 5'-C), 116.20 (7-C + 7'-C), 116.68 (CH), 117.98 (CH), 124.41 (C), 126.17 (C), 131.04 (C), 140.02 (C), 142.50 (C); MS (FAB): *m/z* = 733 (M), $C_{44}H_{51}N_3O_7$ requires 733; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.15; mp > 200°C

**17,17'-Bis(cyclopropylmethyl)-3,3'-(4-phthalimidomethyl)benzyloxy-14,14'-dimethoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(4-(phthalimidomethyl) benzylimino)[7,7'-bimorphinan] (223)**

To a solution of **211** (96 mg, 0.14 mmol) and DMAP (28 mg, 0.23 mmol) in pyridine (5 mL) was added 4,4'-dimethoxytrityl chloride (95 mg, 0.28 mmol) and the reaction mixture was stirred overnight at room temperature. Water was added and the aqueous phase extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated. **222** was isolated as a brown solid and used without any further purification.

$^1$H NMR (270 MHz, $CDCl_3$): 0.05-0.07 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.41-0.45 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.74-0.82 (m, 2H, 2x$NCH_2CH(CH_2CH_2)$), 2.99 (s, 6H, 2x$OCH_3$), 3.70 (s, 12H, 4x$OCH_3$), 5.53 (s, 2H, 5-H +5'-H), 6.41 (d, 2H, *J*=8.1 Hz, 1-H + 1'-H), 6.63 (d, 2H, *J*=8.1 Hz, 2-H + 2'-H), 6.75 (d, 8H, *J*=8.9 Hz), 7.09 (d, 8H, *J*=8.9 Hz), 7.17-7.22 (m, 10H); $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.72

**222** (0.14 mmol), sodium hydride (23 mg, 0.57 mmol) and **206** (0.14 g, 0.42 mmol) were reacted according to the general procedure I. After purification, **223** was isolated as a brown solid (41 mg, 20%).

IR $\nu_{max}$/cm (neat): 2916 (C-H aromatic), 1715 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 0.10 (d, 4H, *J*=4.6 Hz, 2x$NCH_2CH(CHHCHH)$), 0.41-0.53 (m, 4H, 2x$NCH_2CH(CHHCHH)$), 0.77-0.91 (m, 2H, 2x$NCH_2CH(CH_2CH_2)$), 3.11 (s, 6H, 2x$OCH_3$), 4.76 (d, 2H, *J*=12.3 Hz, 2xOC*H*H), 4.81 (s, 6H, 3x$NCH_2$), 4.86 (d, 2H, *J*=12.3 Hz, 2xOCH*H*), 5.23 (s, 2H, 5-H + 5'-H), 5.24 (d, 1H, *J*=16.8 Hz, NC*H*H), 5.31 (d, 1H, *J*=16.8 Hz, NCH*H*), 6.44 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.58 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 6.86 (d, 2H, *J*=8.2 Hz), 7.13 (d, 2H, *J*=8.2 Hz), 7.23 (d, 2H, *J*=8.2 Hz), 7.37 (d, 2H, *J*=8.2 Hz), 7.61-7.65 (m, 6H), 7.70-7.74 (m, 2H), 7.77-7. 81 (m, 4H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 3.15 (2x$NCH_2CH(CH_2CH_2)$), 4.22 (2x$NCH_2CH(CH_2CH_2)$), 9.18 (2x$NCH_2CH(CH_2CH_2)$), 22.43 ($CH_2$), 23.18 ($CH_2$), 30.25 (15-C + 15'-C), 40.86 (Phtha$NCH_2$), 41.32 (2xPhtha$NCH_2$), 44.72 (16-C + 16'-C), 47.28 ($NCH_2Ph$), 48.15 (13-C + 13'-C), 48.67 (14-CO*C*H3 + 14'-CO*C*H3), 55.36 (9-C + 9'-C), 59.44 (18-C + 18'-C), 71.16 (2x$OCH_2Ph$), 78.31 (14-C + 14'-C), 84.53 (5-C + 5'-C), 115.38 (C), 116.66 (CH), 117.76 (CH), 123.19 (CH), 123.25 (CH), 125.75 (C), 126.39 (CH), 126.82 (C), 127.75 (CH), 128.53 (CH), 128.69 (CH), 131.97 (C), 132.05 (C), 133.65 (CH), 133.87 (CH), 134.81 (C), 135.56 (C), 137.43 (C), 138.24 (C), 141.93 (C), 144.62 (C), 167.77 (CO), 167.94 (CO); MS (FAB): *m/z* = 1437 (M); $C_{90}H_{80}N_6O_{12}$ requires 1437; $R_f$ (DCM/MeOH/$NH_4OH$: 110/10/1): 0.75 ; mp : 122°C

**17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-tetraacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(4-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan] (224)**

**178** (0.17 g, 0.20 mmol), sodium hydride (60% in oil, 24 mg, 0.60 mmol), 18-crown-6 (20 mg, 0.08 mmol) and **206** (0.20 g, 0.60 mmol) were reacted according to the general procedure I. **224** was isolated as a brown solid (0.08 g, 37 %).

$^1$H NMR (270 MHz, $CDCl_3$): 0.01-0.05 (m, 4H, 2xNCH$_2$CH(C*H*HC*H*H)), 0.43 (d, 4H, *J*=7.4 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.66-0.78 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 1.85 (s, 3H, $CH_3$), 1.97 (s, 3H, $CH_3$), 4.42 (d, 2H, *J*=5.7 Hz), 4.60-4.98 (m, 2H, NCH$_2$Ph), 4.83 (s, 2H, CH$_2$NPhtha), 5.21 (s, 2H, 5-H +5'-H), 6.61 (d, 2H, *J*=8.2 Hz, 1-H + 1'-H), 6.73 (d, 2H, *J*=8.2 Hz, 2-H + 2'-H), 7.20-7.38 (m, 4H), 7.64-7.71 (m, 2H), 7.78-7.86 (m, 2H); MS (FAB): *m/z* = 1079.4450 (M+H); $C_{64}H_{63}N_4O_{12}$ requires 1079.4442; $R_f$ (DCM/MeOH/$NH_4OH$: 200/12/1): 0.55

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(4-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (227)**

**224** (0.15 g, 0.14 mmol) was dissolved in a mixture of conc. HCl/MeOH (2 mL, 1/1) and the reaction was stirred overnight at 85°C. The mixture was evaporated to dryness and water was added. The aqueous phase was basified to pH=8 with diluted $NH_4OH$ and extracted with DCM/MeOH: 5/1. The organic phase was dried ($MgSO_4$) and the solvent evaporated. Purification by column chromatography (gradient elution, $CHCl_3$/MeOH/$NH_4OH$: 450/10/1 to $CHCl_3$/MeOH/$NH_4OH$: 100/10/1) afforded **227** (66 mg, 52%) and **230** (23 mg, 21%) as brown solids.

Data for **227**:

IR $\nu_{max}$/cm (neat): 3404 (br, bonded OH), 1713 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 0.09 (d, 4H, *J*=4.9 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.49 (d, 4H, *J*=8.0 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.75-0.85 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 3.00 (d, 2H, *J*=18.4 Hz), 3.14 (d, 2H, *J*=6.3 Hz), 3.64-4.20 (br, s, 4H, OH), 4.82 (s, 2H, CH$_2$NPhtha), 5.19 (d, 1H, *J*=17.2 Hz, NC*H*H), 5.29 (s, 2H, 5-H +5'-H), 5.44 (d, 1H, *J*=17.2 Hz, NCH*H*), 6.41-6.48 (m, 4H, 1-H + 1'-H + 2-H + 2'-H), 6.79 (d, 2H, *J*=8.0 Hz, Ar), 7.32 (d, 2H, *J*=8.0 Hz, Ar), 7.66-7.69 (m, 2H, Ar), 7.82-7.85 (m, 2H, Ar);

$^{13}C$ NMR (67.8 MHz, $CDCl_3$): 3.74 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.83 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 9.34 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 22.98 (10-C + 10'-C), 28.91 (8-C + 8'-C), 31.34 (15-C + 15'-C), 41.15 (CH$_2$NPhtha), 43.50 (16-C + 16'-C), 47.05 (NCH$_2$), 47.96 (13-C + 13'-C), 59.29 (18-C + 18'-C), 62.34 (9-C + 9'-C), 72.66 (14-C + 14'-C), 84.74 (5-C + 5'-C), 116.45 (C), 116.66 (CH), 118.45 (CH), 123.26 (CH), 124.99 (C), 125.60 (C), 125.75 (CH), 128.61 (CH), 130.66 (C), 132.19 (C), 133.87 (CH), 134.77 (C), 138.68 (C), 139.61 (C), 142.79 (C), 168.12 (CO); MS (FAB): *m/z* = 911.4004 (M+H); $C_{56}H_{55}N_4O_8$ requires 911.4019; $R_f$ (DCM/MeOH/$NH_4OH$: 110/10/1): 0.31; mp > 220 °C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (228)**

**178** (0.33 g, 0.40 mmol), sodium hydride (60% in oil, 64 mg, 1.60 mmol), 18-crown-6 (20 mg, 0.08 mmol) and **207** (0.40 g, 1.20 mmol) were reacted according to the general procedure I, affording **225** as a brown solid (0.18 g, 42 %).

**225** (80 mg, 74 µmol) was immediately dissolved in a mixture of conc. HCl/MeOH (2mL, 1/1) and the solution was stirred overnight at 86°C. The solvents were then removed by evaporation and water was added. The aqueous phase was basified to pH=10 with diluted $NH_4OH$ and extracted with DCM/MeOH: 5/1. The organic phase was dried ($MgSO_4$) and concentrated under vacuum. Purification by column chromatography, eluting first with $CHCl_3$/MeOH/$NH_4OH$: 450/10/1, then with $CHCl_3$/MeOH/$NH_4OH$: 300/10/1, afforded **228** as a brown solid (47 mg, 70%).

$^1H$ NMR (270 MHz, $CDCl_3$): 0.09 (d, 4H, *J*=4.9 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.49 (d, 4H, *J*=7.9 Hz, 2xNCH$_2$CH(CH*H*CH*H*)), 0.73-0.85 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 1.54 (d, 2H, *J*=8.5 Hz), 3.02 (d, 2H, *J*=18.4 Hz), 3.14 (d, 2H, *J*=6.1 Hz), 4.80 (d, 2H, *J*=14.9 Hz, C*H*HNPhtha), 4.87 (d, 2H, *J*=14.9 Hz, CH*H*NPhtha), 5.25 (d, 1H, *J*=16.5 Hz, NC*H*H), 5.31 (s, 2H, 5-H +5'-H), 5.37 (d, 1H, *J*=16.5 Hz, NCH*H*), 6.45 (d, 2H, *J*=8.1 Hz, 1-H + 1'-H), 6.57 (d, 2H, *J*=8.1 Hz, 2-H + 2'-H), 6.84-6.86 (m, 1H), 7.17-7.39 (m, 3H), 7.65-7.71 (m, 2H), 7.80-7.85 (m, 2H); $^{13}C$ NMR (67.8 MHz, $CDCl_3$): 3.71 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 3.90 (2xNCH$_2$CH(CH$_2$*C*H$_2$)), 9.34 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 22.98 (10-C + 10'-C), 28.91

(8-C + 8'-C), 31.42 (15-C + 15'-C), 41.58 ($CH_2$NPhtha), 43.56 (16-C + 16'-C), 47.47 ($NCH_2$), 47.99 (13-C + 13'-C), 59.27 (18-C + 18'-C), 62.28 (9-C + 9'-C), 72.67 (14-C + 14'-C), 84.86 (5-C + 5'-C), 116.34 (C), 116.89 (CH), 118.50 (CH), 123.48 (CH), 125.07 (C), 125.74 (C), 125.94 (CH), 126.73 (CH), 127.14 (CH), 128.95 (CH), 130.72 (C), 132.00 (C), 134.04 (CH), 136.46 (C), 138.79 (C), 139.51 (C), 143.03 (C), 168.31 (CO); $C_{56}H_{54}N_4O_8$ requires 910.3941; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.38; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(2-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (229)**

**178** (0.33 g, 0.40 mmol), sodium hydride (60% in oil, 64 mg, 1.60 mmol), 18-crown-6 (20 mg, 0.08 mmol) and **208** (0.40 g, 1.20 mmol) were reacted according to the general procedure I, but the reaction mixture was stirred at 90°C for 14 hrs then at room temperature for 48 hrs. The desired product **226** was obtained as a brown solid (0.18 g, 42 %).

**226** (0.13 g, 0.12 mmol) was immediately dissolved in a mixture of conc. HCl/MeOH (2 mL, 1/1) and the reaction was stirred overnight at 85°C. The solvents were then removed and water was added. The aqueous phase was basified to pH=8 with diluted $NH_4OH$ and extracted with DCM/MeOH: 5/1. The organic phase was dried ($MgSO_4$) and concentrated. Purification by column chromatography, eluting first with $CHCl_3$/MeOH/$NH_4OH$: 450/10/1, then with $CHCl_3$/MeOH/$NH_4OH$: 300/10/1, afforded **229** (46 mg, 42%) and **231** (29 mg, 31%) as brown solids.

Data for **229**:

$^1$H NMR (270 MHz, $CD_3OD$): 0.03 (d, 4H, *J*=4.9 Hz, 2xNCH$_2$CH(C*H*HC*H*H)), 0.37-0.44 (m, 4H, 2xNCH$_2$CH(CH*H*CH*H*)), 0.70-0.78 (m, 2H, 2xNCH$_2$C*H*(CH$_2$CH$_2$)), 2.97 (d, 2H, *J*=18.6 Hz), 3.14 (d, 2H, *J*=6.2 Hz), 5.05 (d, 1H, *J*=15.6 Hz, C*H*HNPhtha), 5.12 (d, 1H, *J*=15.6 Hz, CH*H*NPhtha), 5.12 (s, 2H, 5-H + 5'-H), 5.45 (d, 1H, *J*=16.6 Hz, NC*H*H), 5.72 (d, 1H, *J*=16.6 Hz, NCH*H*), 6.39 (d, 2H, *J*=8.0 Hz, 1-H + 1'-H), 6.43 (d, 2H, *J*=8.0 Hz, 2-H + 2'-H), 6.81-6.84 (m, 1H), 7.03-7.14 (m, 2H), 7.22-7.26 (m, 1H), 7.65-7.68 (m, 2H, Phtha), 7.75-7.78 (m, 2H, Phtha); $^{13}$C NMR (67.8 MHz, $CD_3OD$): 4.09 (2xNCH$_2$CH(*C*H$_2$CH$_2$)), 4.61

(2xNCH$_2$CH(CH$_2$*C*H$_2$)), 10.11 (2xNCH$_2$*C*H(CH$_2$CH$_2$)), 23.92 (10-C + 10'-C), 30.00 (8-C + 8'-C), 32.49 (15-C + 15'-C), 39.92 (NCH$_2$Phtha), 44.82 (16-C + 16'-C), 45.65 (CH$_2$), 49.10 (13-C + 13'-C), 60.33 (18-C + 18'-C), 63.36 (9-C + 9'-C), 74.36 (14-C + 14'-C), 85.41 (5-C + 5'-C), 117.07 (C), 117.95 (CH), 119.70 (CH), 124.40 (CH), 125.90 (C), 127.60 (C), 128.11 (CH), 129.26 (CH), 129.43 (CH), 129.47 (CH), 132.30 (C), 133.36 (C), 134.20 (C), 135.49 (CH), 137.99 (C), 141.15 (C), 144.40 (C), 169.95 (CO); MS (FAB): *m/z* = 911 (M); $C_{56}H_{54}N_4O_8$ requires 911; $R_f$ (DCM/MeOH/NH$_4$OH: 110/10/1): 0.40; mp > 220°C

**17,17'-Dimethyl-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (233)**

**237** (0.17 g, 0.20 mmol) was dissolved in a mixture of MeOH/conc. HBr (6 mL, 1/1) and the solution was stirred overnight at room temperature. The solvents were removed by evaporation, water was added and the pH adjusted to pH=12 with diluted NH$_4$OH. The aqueous phase was extracted with DCM/MeOH: 5/1 and the organic phase was dried (MgSO$_4$) and concentrated. The crude product was purified by column chromatography, eluting with CHCl$_3$/MeOH/NH$_4$OH: 250/10/1, which gave **233** as an off white solid (0.125 g, 93 %).

IR $\nu_{max}$/cm (KBr): 3400 (br); $^1$H NMR (270 MHz, CDCl$_3$): 2.35 (s, 6H, 2xNMe), 5.25 (d, 1H, *J*=16.9 Hz, C*H*H), 5.33 (s, 2H, 5-H + 5'-H), 5.50 (d, 1H, *J*=16.9 Hz, CH*H*), 6.50 (d, 2H, *J*=8.1 Hz, 1-H + 1'-H), 6.58 (d, 2H, *J*=8.1 Hz, 2-H + 2'-H), 6.88 (d, 2H, *J*=6.7 Hz), 7.24-7.37 (m, 3H); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 22.34 (CH$_2$), 28.97 (CH$_2$), 31.23 (CH$_2$), 42.94 (NMe), 45.28 (CH$_2$), 47.35 (CH$_2$), 47.43 (13-C + 13'-C), 64.92 (9-C + 9'-C), 73.02 (14-C + 14'-C), 84.89 (5-C + 5'C), 116.32 (C), 116.88 (CH), 118.71 (CH), 125.23 (C), 125.61 (CH), 125.67 (C), 126.85 (CH), 128.65 (CH), 130.56 (C), 138.75 (C), 140.02 (C), 142.91 (C); MS (FAB): *m/z* = 672.3063 (M+H); $C_{41}H_{42}N_3O_6$ requires 672.3073; $R_f$ (DCM/MeOH/NH$_4$OH: 110/10/1): 0.27; Anal. ($C_{41}H_{41}N_3O_6$:2HCl:4H$_2$O) requires C 60.32 %, H 6.29 %, N 5.14 %, found: C 60.30 %, H 6.05 %, N 4.81 %; mp > 240°C

**17,17'-Dimethyl-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (235)** [102]

**218** (0.66 g, 2.21 mmol), hydrazine sulfate (0.15 g, 1.15 mmol) and methanesulfonic acid (0.07 mL, 1.08 mmol) were reacted according to the general procedure K, the reaction being however stirred in DMF at 105°C overnight. After purification, **235** was isolated as a brown solid (0.48 g, 75 %).

IR $\nu_{max}$/cm (KBr): 3413 (br, bonded OH); $^1$H NMR (270 MHz, $CDCl_3$): 2.36 (s, 3H, N-Me), 5.60 (s, 2H, 5-H and 5'-H), 6.52 (d, 2H, *J*=8.0 Hz, 1-H and 1'-H), 6.67 (d, 2H, *J*=8.0 Hz, 2-H and 2'-H); $^{13}$C NMR (100.5 MHz, $CDCl_3$): 22.35 ($CH_2$), 28.78 ($CH_2$), 31.37 ($CH_2$), 42.96 (2xN-Me), 45.27 ($CH_2$), 47.27 (13-C + 13'-C), 64.88 (9-C + 9'-C), 73.11 (14-C + 14'-C), 85.59 (5-C + 5'-C), 116.46, 117.56, 118.97, 125.03, 125.15, 130.34, 138.81, 142.83; MS (FAB): *m/z* = 582.2583 (M+H); $C_{34}H_{36}N_3O_6$ requires 582.2608; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.19; mp > 220°C

**17,17'-Dimethyl-3,3'-dibenzyloxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(benzylimino)[7,7'-bimorphinan]-14,14'-diol (237)**

**235** (0.16 g, 0.31 mmol), sodium hydride (0.12 g, 3.0 mmol), 18-crown-6 (33 mg, 0.12 mmol) and benzyl bromide (0.19 mL, 1.59 mmol) were reacted according to the general procedure I, but the reaction was carried out at room temperature. The crude oil was purified by column chromatography (gradient elution, with 100% $CHCl_3$ then $CHCl_3$/MeOH/$NH_4OH$: 400/10/1 to 400/25/1) to yield **237** as a brown solid (0.23 g, 87 %).

$^1$H NMR (270 MHz, $CDCl_3$): 2.35 (s, 6H, 2xNMe), 4.95 (s, 4H, 2x$OCH_2$), 5.29 (s, 2H, 5H + 5'-H), 5.31-5.42 (m, 2H, $NCH_2$), 6.52 (d, 2H, *J*=8.3 Hz, 1-H + 1'-H), 6.66 (d, 2H, *J*=8.3 Hz, 2-H + 2'-H), 6.97-7.06 (m, 1H), 7.13 (d, 4H, *J*=4.5 Hz), 7.24-7.35 (m, 10H); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 22.26 ($CH_2$), 28.94 ($CH_2$), 31.45 ($CH_2$), 42.88 (NMe), 45.23 ($CH_2$), 47.05 (13-C + 13'-C), 47.61 ($CH_2$), 64.86 (9-C + 9'-C), 71.42 ($OCH_2$), 72.82 (14-C + 14'-C), 84.41 (5-C + 5'C), 115.79 (C), 116.46 (CH), 118.17 (CH), 125.84 (C), 126.09 (C), 126.72 (CH), 127.56 (CH), 128.26 (CH), 131.22 (C), 137.63 (C), 138.33 (C), 142.19 (C), 144.87 (C); MS (FAB): *m/z* = 852 (M); $C_{55}H_{53}N_3O_6$ requires 852; mp > 240°C

**17,17'-Dimethyl-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-3,3'-diol (239)** [102]

**217** (1.45 g, 4.51 mmol), hydrazine sulfate (0.31 g, 2.38 mmol) and methanesulfonic acid (0.14 mL, 2.16 mmol) were reacted according to the general procedure K. After purification by column chromatography, **239** was isolated as a brown solid (0.43 g, 35 %).

IR $\nu_{max}$/cm (KBr): 3380 (br, bonded OH); $^1$H NMR (270 MHz, $CDCl_3$): 1.57-1.79 (m, 3H), 1.97 (dd, 1H, *J*=14.7 Hz and 5.6 Hz), 2.10-2.40 (m, 5H), 2.22 (s, 3H, NMe), 2.82 (d, 1H, *J*=18.5 Hz), 2.98-3.01 (m, 1H), 5.20 (s, 2H, 5H and 5'-H), 6.33 (d, 2H, *J*=8.2 Hz, 1-H and 1'-H), 6.39 (d, 2H, *J*=8.2 Hz, 2-H and 2'-H); $^{13}$ C NMR (67.8 MHz, $CDCl_3$): 20.26 (2x$CH_2$), 20.93 (2x$CH_2$), 34.99 (15-C + 15'-C), 40.58 (14-C + 14'-C), 42.11 (2xNMe), 42.97 (13-C + 13'-C), 46.40 (16-C + 16'-C), 59.56 (9-C + 9'-C), 85.44 (5-C + 5'-C), 116.29 (CH), 116.86 (C), 118.39 (CH), 124.99 (C), 125.09 (C), 128.44 (C), 139.21 (C), 143.25 (C); MS (FAB): *m/z* = 550.2702 (M+H); $C_{34}H_{36}N_3O_4$ requires 550.2705; $R_f$ (DCM/MeOH/$NH_4OH$: 100/16/1.6): 0.13; mp > 240°C

**17,17'-Dimethyl-3,3'-dibenzyloxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(benzylimino)[7,7'-bimorphinan] (240)**

**239** (0.13 g, 0.24 mmol), sodium hydride (90 mg, 2.25 mmol), 18-crown-6 (30 mg, 0.11 mmol) and benzyl bromide (0.14 mL, 1.18 mmol) were reacted according to the general procedure I, but the reaction was carried out at room temperature. The crude oil was purified by column chromatography (gradient elution with 100% $CHCl_3$ then $CHCl_3$/MeOH/$NH_4OH$: 400/10/1 to 400/25/1) to yield **240** as a brown solid (37 mg, 19 %).

$^1$H NMR (270 MHz, $CDCl_3$): 2.39 (s, 6H, 2xNMe), 3.00 (d, 2H, *J*=18.5 Hz), 3.14-3.19 (m, 2H), 4.96 (s, 4H, 2x$OCH_2$), 5.26 (s, 2H, 5-H and 5'-H), 5.29 (d, 1H, *J*=16.3 Hz, NC*H*H), 5.37 (d, 1H, *J*=16.3 Hz, NCH*H*), 6.55 (d, 2H, *J*=8.2 Hz, 1-H and 1'-H), 6.69 (d, 2H, *J*=8.2 Hz, 2-H and 2'-H), 7.04-7.13 (m, 5H), 7.24-7.33 (m, 10H); $^{13}$ C NMR (67.8 MHz, $CDCl_3$): 20.46 ($CH_2$), 21.45 ($CH_2$), 35.83 (15-C + 15'-C), 41.18 (C), 42.88 (2xNMe), 43.33 (C), 46.65 ($CH_2$), 47.63 ($CH_2$), 59.77 (9-C + 9'-C), 71.65 ($OCH_2$), 85.08 (5-C + 5'-C), 116.65 (CH), 117.65 (C), 118.51 (CH), 126.69 (CH),

126.96 (CH), 127.57 (CH), 127.62 (CH), 128.24 (CH), 128.35 (CH), 129.68 (C), 137.58 (C), 138.27 (C), 141.87 (C), 145.08 (C); MS (FAB): *m/z* = 820 (M); $C_{55}H_{53}N_3O_4$ requires 820; $R_f$ (DCM/MeOH/$NH_4OH$: 100/10/1): 0.43

**17,17'-Dimethyl-3,3'-dimethoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (242)**

Hydrocodone hydrochloride (1.81g, 5.39 mmol), hydrazine sulfate (0.31 g, 2.84 mmol) and methanesulfonic acid (0.34 mL, 5.26 mmol) were reacted according to the general procedure K. After purification by column chromatography, **242** was isolated as a brown solid (1.10 g, 71 %).

$^1$H NMR (270 MHz, $CDCl_3$): 2.39 (s, 6H, 2x$NCH_3$), 3.79 (s, 6H, 2x$OCH_3$), 5.39 (s, 2H, 5-H and 5'-H), 6.59 (d, 2H, *J*=8.3 Hz, 1-H and 1'-H), 6.66 (d, 2H, *J*=8.3 Hz, 2-H and 2'-H), 8.09 (br, s, 1H, NH); $^{13}$ C NMR (100.5 MHz, $CDCl_3$): 19.82 (2x$CH_2$), 20.73 (2x$CH_2$), 35.37 (15-C + 15'-C), 40.74 (14-C + 14'-C), 42.45 (2x$NCH_3$), 42.86 (13-C + 13'-C), 46.11 (16-C + 16'-C), 55.48 (2x$OCH_3$), 59.22 (9-C + 9'-C), 85.35 (5-C + 5'-C), 112.28 (CH), 117.00 (C), 117.79 (CH), 125.13 (C), 126.72 (C), 128.67 (C), 142.22 (C), 144.10 (C)

**4-Phthalimidotoluene (244)** [216]

A solution of toluidine (4.28 g, 40 mmol) and phthalic anhydride (5.91 g, 40 mmol) in acetic acid (80 mL) was refluxed for two hours. The reaction mixture was then cooled down to room temperature and poured into water. The precipitate was filtered off, washed with water, dissolved in DCM and dried over $MgSO_4$. The solvent was removed by evaporation to yield **244** (8.0 g, 84 %) as an off-white solid.

IR $\nu_{max}$/cm (KBr): 1709 (CO); $^1$H NMR (400 MHz, $CDCl_3$): 2.39 (s, 3H, $CH_3$), 7.28-7.30 (m, 4H), 7.73-7.75 (m, 2H), 7.90-7.92 (m, 2H); $^{13}$ C NMR (100.5 MHz, $CDCl_3$): 21.10 ($CH_3$), 123.54 (CH), 126.35 (CH), 128.89 (C), 129.66 (CH), 131.69 (C), 134.21 (CH), 138.03 (C), 167.30 (CO); MS (FAB): *m/z* = 238.0860 (M+H); $C_{15}H_{12}NO_2$ requires 238.0867; $R_f$ (*n*-hexanes/ethyl acetate: 4/1): 0.22; mp : 193-194°C (lit.: 201-203°C) [216]

***N*-(4-Phthalimidobenzyl)carbazole (247)**

Carbazole (167 mg, 1.0 mmol), sodium hydride (80 mg, 2.0 mmol), 15-crown-5 (0.02 mL, 0.1 mmol) and **182** (0.35 g, 1.1 mmol) in dry DMF (5 mL) were reacted according to the general procedure I. After purification by column chromatography, **247** was isolated as a brown solid (0.15 g, 37%).

$^1$H NMR (270 MHz, $CDCl_3$): 5.51 (s, 2H, $CH_2$), 7.17-7.20 (m, 4H), 7.25-7.29 (m, 2H), 7.31 (d, 2H, *J*=7.9 Hz), 7.35-7.41 (m, 2H), 7.69-7.72 (m, 2H, Phtha), 7.84-7.88 (m, 2H, Phtha), 8.08 (d, 2H, *J*=7.9 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 46.19 ($CH_2$), 108.93 (CH), 119.45 (CH), 120.49 (CH), 123.14 (C), 123.85 (CH), 126.03 (CH), 126.93 (CH), 127.12 (CH), 131.72 (C), 134.53 (CH), 140.61 (C), 167.33 (CO); mp : 187 °C

***N*-(4-Aminobenzyl)-carbazole (248)**

To a solution of **247** (49 mg, 0.12 mmol) in ethanol (1 mL) was added DCM until the solution became completely clear. Hydrazine hydrate (11.6 µL, 0.37 mmol) was added and the reaction mixture stirred for two days. The solvent was then removed under vacuum and the crude product purified by column chromatography. **248** was isolated as a brown solid (19 mg, 57%).

$^1$H NMR (270 MHz, $CDCl_3$): 3.50 (br, s, 2H, $NH_2$), 5.32 (s, 2H, $CH_2$), 6.48 (d, 2H, *J*=6.5 Hz), 6.88 (d, 2H, *J*=6.5 Hz), 7.12-7.18 (m, 2H), 7.28-7.38 (m, 2H), 8.04 (d, 2H, *J*=7.9 Hz); $^{13}$C NMR (67.8 MHz, $CDCl_3$): 46.15 ($CH_2$), 108.96 (CH), 115.24 (CH), 118.95 (CH), 120.27 (CH), 122.89 (C), 125.70 (CH), 127.01 (C), 127.63 (CH), 140.61 (C), 145.63 (C)

**17-Methyl-6,7-didehydro-4,5α-epoxy-3-methoxy-14-acetoxy-indolo[2',3':6,7]-morphinan (249)**

A solution of 17-methyl-6,7-didehydro-4,5α-epoxy-3-methoxy-14-hydroxy-indolo[2',3':6,7]-morphinan (0.13 g, 0.33 mmol) in acetic anhydride (10 mL) was treated according to the same method as used for the preparation of **178**. Purification by column chromatography, eluting first with $CHCl_3$ then with $CHCl_3$/MeOH/$NH_4OH$: 400/5/1, afforded **249** as an off-white solid (0.142 g, 98%).

IR $\nu_{max}$/cm (KBr): 1705 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 1.92 (s, 3H, $OCOCH_3$), 2.34 (s, 3H, $NCH_3$), 3.25 (d, 1H, *J*=18.6 Hz), 3.74 (s, 3H, 3-$COCH_3$), 3.75 (d, 1H, *J*=16.8 Hz), 4.40 (d, 1H, *J*=6.2 Hz), 5.64 (s, 1H, 5-H), 6.58-6.64 (m, 2H, 1-H and 2-H), 6.99-7.05 (m, 1H, 5'-H), 7.12-7.18 (m, 1H, 6'-H), 7.30 (d, 1H, *J*=8.1 Hz, 7'-H), 7.39 (d, 1H, *J*=7.4 Hz, 4'-H), 8.17 (br, s, 1H, NH); $^{13}$ C NMR (67.8 MHz, $CDCl_3$): 22.37 ($OCOCH_3$), 22.69 ($CH_2$), 24.48 ($CH_2$), 30.85 ($CH_2$), 42.83 (NMe), 45.52 (16-C), 47.63 (13-C), 55.92 (OMe), 58.02 (9-C), 83.93 (14-C), 84.91 (5-C), 110.58 (C), 111.25 (CH), 113.06 (CH), 118.60 (CH), 118.92 (CH), 119.26 (CH), 122.73 (CH), 126.52 (C), 126.55 (C), 129.08 (C), 129.76 (C), 136.89 (C), 143.10 (C), 143.95 (C), 170.72 (CO); mp > 210°C

**17-Methyl-6,7-didehydro-4,5α-epoxy-3-methoxy-14-acetoxy-(4-(phthalimido methyl)benzylindolo)[2',3':6,7]-morphinan (251)**

**249** (72 mg, 0.17 mmol), sodium hydride (60% in oil, 27 mg, 0.67 mmol), 15-crown-5 (0.01 mL, 0.05 mmol) and **182** (0.17 g, 0.51 mmol) in dry DMF (5 mL) were reacted according to the general procedure I. After purification by column chromatography, eluting first with $CHCl_3$ then with $CHCl_3$/MeOH/$NH_4OH$: 400/5/1, **251** was obtained as a brown solid (34 mg, 31%).

IR $\nu_{max}$/cm (KBr): 1760, 1715 (CO); $^1$H NMR (270 MHz, $CDCl_3$): 1.91 (s, 3H, $OCOCH_3$), 2.34 (s, 3H, $NCH_3$), 3.26 (d, 1H, *J*=18.3 Hz), 3.72 (s, 3H, 3-$COCH_3$), 3.80 (d, 1H, *J*=16.5 Hz), 4.41 (d, 1H, *J*=5.7 Hz), 5.56 (d, 1H, *J*=17.3 Hz, NC*H*H), 5.63 (d, 1H, *J*=17.3 Hz, NCH*H*), 5.64 (s, 1H, 5-H)), 6.60 (d, 1H, *J*=8.2 Hz, 1-H), 6.64 (d, 1H, *J*=8.2 Hz, 2-H), 7.00-7.07 (m, 1H, 5'-H), 7.12-7.15 (m, 3H, 6'-H + 2Ar), 7.31-7.34 (m, 3H, 7'-H + 2Ar), 7.43 (d, 1H, *J*=7.6 Hz, 4'-H), 7.74-7.79 (m, 2H), 7.90-7.94 (m, 2H); $^{13}$ C NMR (67.8 MHz, $CDCl_3$): 22.42 ($OCOCH_3$), 22.77 ($CH_2$), 24.72 ($CH_2$), 31.02 ($CH_2$), 42.88 (NMe), 45.56 (16-C), 46.76 ($NCH_2Ph$), 47.87 (13-C), 56.23 (OMe), 58.08 (9-C), 84.02 (14-C), 84.07 (5-C), 110.03 (CH), 110.35 (C), 113.74 (CH), 118.68 (CH), 119.17 (CH), 119.40 (CH), 122.83 (CH), 123.75 (CH), 126.49 (C), 126.56 (C), 126.65 (CH), 126.85 (CH), 130.05 (C), 130.40 (C), 130.66 (C), 131.71 (C), 134.42 (CH), 137.32 (C), 138.05 (C), 143.26 (C), 144.06 (C), 167.27 (CO), 170.69 (CO); mp > 215°C

# 5. REFERENCES


1. Gulland, J. M.; Robinson, R. The morphine group. Part I. A discussion of the constitutional problem. *J. Chem. Soc.* **1923**, *123*, 980-998.

2. Gates, M.; Tschudi, G. The synthesis of morphine. *J. Am. Chem. Soc.* **1952**, *74*, 1109-1110.

3. Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517-532.

4. Gilbert, P. E.; Martin, W. R. The effects of morphine- and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 66-82.

5. Lord, J. A.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W. Endogenous opioid peptides: multiple agonists and receptors. *Nature* **1977**, *267*, 495-499.

6. Yasuda, K.; Raynor, K.; Kong, H.; Breder, C. D.; Takeda, J.; Reisine, T.; Bell, G. I. Cloning and functional comparison of κ and δ opioid receptors from mouse brain. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6736-6740.

7. Wang, J. -B.; Johnson, P. S.; Persico, A. M.; Hawkins, A. L.; Griffin, C. A.; Uhl, G. R. Human μ opiate receptor. cDNA and genomic clones, pharmacologic characterization and chromosomal assignment. *FEBS Lett.* **1994**, *338*, 217-222.

8. Kieffer, B. L.; Befort, K.; Gaveriaux-Ruff, C.; Hirth, C. G. The δ-opioid receptor: isolation of a cDNA by expression cloning and pharmacological characterization. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 12048-12052.

9. Pasternak, G. W.; Wood, P. J. Minireview: Multiple mu opiate receptors. *Life Sci.* **1986**, *38*, 1889-1898.

10. Traynor, J. R.; Elliott, J. δ-Opioid receptor subtypes and cross-talk with μ-receptors. *Trends Pharmacol. Sci.* **1993**, *14*, 84-86.

11. Wollemann, M.; Benyhe, S.; Simon, J. The kappa-opioid receptor: evidence for the different subtypes. *Life Sci.* **1993**, *52*, 599-611.

12. Buzas, B.; Rosenberger, J.; Cox, B. M. Mu and delta opioid receptor gene expression after chronic treatment with opioid agonist. *Neuroreport* **1996**, *7*, 1505-1508.

13. Fujii, H.; Narita, M.; Mizoguchi, H.; Hirokawa, J.; Kawai, K.; Tanaka, T.; Tseng, L. F.; Nagase, H. Rationale drug design and synthesis of a selective ε opioid receptor antagonist on the basis of the accessory site concept. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4241-4243.

14. Fujii, H.; Narita, M.; Mizoguchi, H.; Murachi, M.; Tanaka, T.; Kawai, K.; Tseng, L. F.; Nagase, H. Drug design and synthesis of ε opioid receptor agonist: 17-(cyclopropylmethyl)-4,5α-epoxy-3,6β-dihydroxy-6,14-endoethenomorphinan -7α-(*N*-methyl-*N*-phenethyl)carboxamide (TAN-821) inducing antinociception mediated by putative opioid ε receptor. *Bioorg. Med. Chem.* **2004**, *12*, 4133-4145 and references therein.

15. Civelli, O. Functional genomics: the search for novel neurotransmitters and neuropeptides. *FEBS Lett.* **1998**, *430*, 55-58.

16. Bhushan, R. G.; Sharma, S. K.; Xie, Z.; Daniels, D. J.; Portoghese, P. S. A bivalent ligand (KDN-21) reveals spinal δ and κ opioid receptors are organized as heterodimers that give rise to $\delta_1$ and $\kappa_2$ phenotypes. Selective targeting of δ-κ heterodimers. *J. Med. Chem.* **2004**, *47*, 2969-2972.

17. Poonyachoti, S.; Portoghese, P. S.; Brown, D. R. Characterization of opioid receptors modulating neurogenic contractions of circular muscle from porcine

ileum and evidence that δ- and κ-opioid receptors are coexpressed in myenteric neurons. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 69-77.

18. Jordan, B. A.; Devi, L. A. G-protein-coupled receptor heterodimerization modulates receptor function. *Nature* **1999**, *399*, 697-700.

19. Portoghese, P. S.; Lin, C. -E.; Farouz-Grant, F.; Takemori, A. E. Structure-activity relationship of N17'-substituted norbinaltorphimine congeners. Role of the N17' basic group in the interaction with a putative address subsite on the κ opioid receptor. *J. Med. Chem.* **1994**, *37*, 1495-1500.

20. Neumeyer, J. L.; Zhang, A.; Xiong, W.; Gu, X. -H.; Hilbert, J. E.; Knapp, B. I.; Negus, S. S.; Mello, N. K.; Bidlack, J. M. Design and synthesis of novel dimeric morphinan ligands for κ and μ opioid receptors. *J. Med. Chem.* **2003**, *46*, 5162-5170 and references therein.

21. Dean, M. K.; Higgs, C.; Smith, R. E.; Bywater, R. P.; Snell, C. R.; Scott, P. D.; Upton, G. J. G.; Howe, T. J.; Reynolds, C. A. Dimerization of G-protein-coupled receptors. *J. Med. Chem.* **2001**, *44*, 4595-4614.

22. Metzger, T. G.; Paterlini, M. G.; Ferguson, D. M.; Portoghese, P. S. Investigation of the selectivity of oxymorphone- and naltrexone-derived ligands via site-directed mutagenesis of opioid receptors: exploring the 'address' recognition locus. *J. Med. Chem.* **2001**, *44*, 857-862.

23. Metzger, T. G.; Ferguson, D. M. On the role of extracellular loops of opioid receptors in conferring ligand selectivity. *FEBS Lett.* **1995**, *375*, 1-4.

24. Seki, T.; Minami, M.; Nakagawa, T.; Ienaga, Y.; Morisada, A.; Satoh, M. DAMGO recognizes four residues in the third extracellular loop to discriminate between μ- and κ-opioid receptors. *Eur. J. Pharmacol.* **1998**, *350*, 301-310.

25. Sharma, S. K.; Jones, R. M.; Metzger, T. G.; Ferguson, D. M.; Portoghese, P. S. Transformation of a κ-opioid receptor antagonist to a κ-agonist by transfer of a guanidinium group from the 5'- to 6'-position of naltrindole. *J. Med. Chem.* **2001**, *44*, 2073-2079.

26. Mestek, A.; Chen, Y.; Yu, L. Mu opioid receptors: cellular action and tolerance development. *NIDA Res. Monogr.* **1996**, *161*, 104-126.

27. Hjorth, S. A.; Thirstrup, K.; Grandy, D. K.; Schwartz, T. W. Analysis of selective binding epitopes for the κ-opioid receptor antagonist nor-binaltorphimine. *Am. Soc. Pharmacol. Exp. Ther.* **1995**, *47*, 1089-1094.

28. Eguchi, M. Recent advances in selective opioid receptor agonists and antagonists. *Med. Res. Rev.* **2004**, *24*, 182-212.

29. Christo, P. J.; Grabow, T. S.; Raja, S. N. Opioid effectiveness, addiction, and depression in chronic pain. *Pain and Depression* **2004**, *25*, 123-137 and references therein.

30. Qiu, Y.; Law, P. -Y.; Loh, H. H. μ-Opioid receptor desensitization. *J. Biol. Chem.* **2003**, *278*, 36733-36739.

31. Bohn, L. M.; Gainetdinov, R. R.; Lin, F. -T.; Lefkowitz, R. J.; Caron, M. G. μ-Opioid receptor desensitization by β-arrestin-2 determines morphine tolerance but not dependence. *Nature* **2000**, *408*, 720-723.

32. Pan, Z. Z. μ-Opposing actions of the κ-opioid receptor. *Trends Pharmacol. Sci.* **1998**, *19*, 94-98 and references therein.

33. Whistler, J. L.; Chuang, H. -H.; Chu, P.; Jan, L. Y.; von Zastrow, M. Functional dissociation of μ opioid receptor signaling and endocytosis: implications for the biology of opiate tolerance and addiction. *Neuron* **1999**, *23*, 737-746.

34. Nestler, E. J. Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. *Trends Pharmacol. Sci.* **2004**, *25*, 210-218.

35. Raith, K.; Hochhaus, G. Drugs used in the treatment of opioid tolerance and physical dependence: a review. *Int. J. Clin. Pharmacol. Ther.* **2004**, *42*, 191-203.

36. Koob, G. F.; Sanna, P. P.; Bloom, F. E. Neuroscience of addiction. *Neuron* **1998**, *21*, 467-476.

37. Petukhov, P. A.; Zhang, J.; Kozikowski, A. P.; Wang, C. Z.; Ye, Y. P.; Johnson, K. M.; Tella, S. R. SAR studies of piperidine-based analogues of cocaine. 4. Effect of N-modification and ester replacement. *J. Med. Chem.* **2002**, *45*, 3161-3170.

38. Archer, S.; Glick, S. D.; Bidlack, J. M. Cyclazocine revisited. *Neurochem. Res.* **1996**, *21*, 1369-1373.

39. Mague, S. D.; Pliakas, A. M.; Todtenkopf, M. S.; Tomasiewicz, H. C.; Zhang, Y.; Stevens Jr, W. C.; Jones, R. M.; Portoghese, P. S.; Carlezon Jr, W. A. Antidepressant-like effects of κ-opioid receptor antagonists in the forced swim test in rats. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 323-330.

40. Stahl, S. M. Essential Psychopharmacology. Neuroscientific basis and practical applications. Cambridge University Press, **2000**, Chapter *13*, p 499-538.

41. Martin, T. J.; Eisenach, J. C. Pharmacology of opioid and nonopioid analgesics in chronic pain states. *J. Pharm. Exp. Ther.* **2001**, *299*, 811-817.

42. Kim, K. W.; Eun, Y. A.; Soh, S. M.; Eun, J. S.; Cho, K. P. Ligand binding profiles of U-69,593-sensitive and -insensitive sites in human cerebral cortex membranes: Evidence of kappa opioid receptors heterogeneity. *Life Sci.* **1996**, *58*, 1671-1679.

43. Vanderah, T. W.; Schteingart, C. D.; Trojnar, J.; Junien, J. -L.; Lai, J.; Rivière, P. J. -M. FE200041 (D-Phe-D-Phe-D-Nle-D-Arg-$NH_2$): a peripheral efficacious κ opioid agonist with unprecedented selectivity. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 326-333.

44. Snyder, S. H.; Pasternak, G. W. Historical Review: opioid receptors. *Trends Pharmacol. Sci.* **2003**, *24*, 198-205 and references therein.

45. Pfeiffer, A.; Brantl, V.; Herz, A.; Emrich, H. M. Psychotomimesis mediated by κ opiate receptors. *Science* **1986**, *233*, 774-776.

46. Martin, W. R.; Gorodetzky, C. W.; McLane, T. K. An experimental study in the treatment of narcotic addicts with cyclazocine. *Clin. Pharmacol. Ther.* **1966**, 455-464.

47. Walsh, S. L.; Strain, E. C.; Abreu, M. E. Enadoline, a selective kappa opioid agonist: comparison with butorphanol and hydromorphone in humans. *Psychopharmacology* **2001**, *157*, 151-162 and references therein.

48. Liu, B. -H.; Mo, P.; Zhang, S. -B. Effects of mu and kappa opioid receptor agonists and antagonists on contraction of isolated colon strips of rats with cathartic colon. *World J. Gastro.* **2004**, *10*, 1672-1674.

49. Shen, S.; Ingenito, A. J. κ-Opioid receptors behind the blood-brain barrier are involved in the anti-hypertensive effects of systemically administered κ-agonists in the conscious spontaneously hypertensive rat. *J. Pharm. Pharmacol.* **1999**, *51*, 1251-1256.

50. Birch, P. J.; Rogers, H.; Hayes, A. G.; Hayward, N. J.; Tyers, M. B.; Scopes, D. I. C.; Naylor, A.; Judd, D. B. Neuroprotective actions of GR89696, a highly potent and selective κ-opioid receptor agonist. *Br. J. Pharmacol.* **1991**, *103*, 1819-1823.

51. Arjune, D.; Bodnar, R. J. Suppression of nocturnal, palatable and glucoprivic intake in rats by the κ opioid antagonist, nor-binaltorphimine. *Brain Res.* **1990**, *534*, 313-316 and references therein.

52. Husbands, S. M. Kappa-opioid receptor ligands. *Expert Opin. Ther. Patents* **2004**, *14*, 1725-1741.

53. Guéniau, C.; Oberlander, C. The kappa opioid agonist niravoline decreases brain edema in the mouse middle cerebral artery occlusion model of stroke. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 1-6.

54. Obara, I.; Mika, J.; Schäfer, M. K. -H.; Przewlocka, B. Antagonists of the κ-opioid receptor enhance allodynia in rats and mice after sciatic nerve ligation. *Br. J. Pharmacol.* **2003**, *140*, 538-546 and references therein.

55. Xu, M.; Petraschka, M.; McLaughlin, J. P.; Westenbroek, R. E.; Caron, M. G.; Lefkowitz, R. J.; Czyzyk, T. A.; Pintar, J. E.; Terman, G. W.; Chavkin, C. Neuropathic pain activates the endogenous κ opioid system in mouse spinal cord and induces opioid receptor tolerance. *J. Neurosci.* **2004**, *24*, 4576-4584.

56. Mello, N. K.; Negus, S. S. Effects of kappa opioid agonists on cocaine- and food-maintained responding by rhesus monkeys. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 812-824 and reference 39 therein.

57. Shippenberg, T. S.; LeFevour, A.; Heidbreder, C. κ-Opioid receptor agonists prevent sensitization to the conditioned rewarding effects of cocaine. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 545-554.

58. Holden Ko, M. C.; Tuchman, J. E.; Johnson, M. D.; Wiesenauer, K.; Woods, J. H. Local administration of mu or kappa opioid agonists attenuates capsaicin-induced thermal hyperalgesia via peripheral opioid receptors in rats. *Psychopharmacology* **2000**, *148*, 180-185.

59. Rivière, P. J. -M. Peripheral kappa-opioid agonists for visceral pain. *Br. J. Pharmacol.* **2004**, *141*, 1331-1334.

60. Joshi, S. K.; Su, X.; Porreca, F.; Gebhart, G. F. κ-Opioid receptor agonists modulate visceral nociception at a novel, peripheral site of action. *J. Neur.* **2000**, *20*, 5874-5879.

61. Ko, M. -C.; Butelman, E. R.; Woods, J. H. Activation of peripheral κ opioid receptors inhibits capsaicin-induced thermal nociception in rhesus monkeys. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 378-385.

62. Vink, R.; Portoghese, P. S.; Faden, A. I. κ-Opioid antagonist improves cellular bioenergetics and recovery after traumatic brain injury. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **1991**, *261*, 1527-1532.

63. Newman, D. D.; Rajakumar, N.; Flumerfelt, B. A.; Stoessl, A. J. A kappa opioid antagonist blocks sensitization in a rodent model of Parkinson's disease. *Neuroreport* **1997**, *8*, 669-672.

64. Katafuchi, T.; Hattori, Y.; Nagatomo, I.; Koizumi, K. κ-Opioid antagonist strongly attenuates drinking of genetically polydipsic mice. *Brain Res.* **1991**, *546*, 1-7.

65. Porsolt, R. D.; Le Pichon, M.; Jalfre, M. Depression: a new animal model sensitive to antidepressant treatments. *Nature* **1977**, *266*, 730-732.

66. Rothman, R. B.; Gorelick, D. A.; Heishman, S. J.; Eichmiller, P. R.; Hill, B. H.; Norbeck, J.; Liberto, J. G. An open-label study of a functional opioid κ antagonist in the treatment of opioid dependence. *J. Subst. Abuse Treat.* **2000**, *18*, 277-281.

67. Bates, J. J.; Foss, J. F.; Murphy, D. B. Are peripheral opioid antagonists the solution to opioid side effects? *Anesth. Analg.* **2004**, *98*, 116-122.

68. Bohn, L. M.; Gainetdinov, R. R.; Lin, F. -T.; Lefkowitz, R. J.; Caron, M. G. μ-Opioid receptor desensitization by β-arrestin-2 determines morphine tolerance but not dependence. *Nature* **2000**, *408*, 720-723 and references therein.

69. Wentland, M. P.; Ye, Y.; Cioffi, C. L.; Lou, R.; Zhou, Q.; Guoyou, X.; Duan, W.; Dehnhardt, C. M.; Sun, X.; Cohen, D. J.; Bidlack, J. M. Syntheses and opioid receptor binding affinities of 8-amino-2,6-methano-3-benzazocines. *J. Med. Chem.* **2003**, *46*, 838-849.

70. Le Bourdonnec, B.; Belanger, S.; Cassel, J. A.; Stabley, G. J.; DeHaven, R. N.; Dolle, R. E. *trans*-3,4-Dimethyl-4-(3-carboxamidophenyl)piperidines: a novel class of μ-selective opioid antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4459-4462.

71. Streaty, R. A.; Klee, W. A. Deoxymorphines: role of the phenolic hydroxyl in antinociception and opiate receptor interactions. *J. Med. Chem.* **1979**, *22*, 256-259.

72. Zhao, S. Z.; Chung, F.; Hanna, D. B.; Raymundo, A. L.; Cheung, R. Y.; Chen, C. Dose-response relationship between opioid use and adverse effects after ambulatory surgery. *J. Pain Symptom Manage.* **2004**, *28*, 35-46.

73. Mather, L. E. Trends in the pharmacology of opioids: implications for the pharmacotherapy of pain. *Eur. J. Pain* **2001**, *5*, 49-57.

74. Palczewski, K.; Kumasaka, T.; Hori, T.; Behnke, C. A.; Motoshima, H.; Fox, B. A.; Le Trong, I.; Teller, D. C.; Okada, T.; Stenkamp, R. E.; Yamamoto, M.; Miyano, M. Crystal structure of rhodopsin: a G protein-coupled receptor. *Science* **2000**, *289*, 739-745.

75. Filizola, M.; Villar, H. O.; Loew, G. H. Molecular determinants of non-specific recognition of δ, μ, and κ opioid receptors. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 69-76 and references terein.

76. Thomas, J. B.; Atkinson, R. N.; Namdev, N.; Rothman, R. B.; Scott, E. F.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y. -F.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of the first *trans*-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)-piperidine derivative to possess highly potent and selective opioid κ receptor antagonist activity. *J. Med. Chem.* **2001**, *44*, 2687-2690.

77. Hughes, J.; Smith, T.; Morgan, B.; Fothergill, L. Purification and properties of enkephalin – the possible endogenous ligand for the morphine receptor. *Life Sci.* **1975**, *16*, 1753-1758.

78. Lu, Y.; Nguyen, T. M. -D.; Weltrowska, G.; Berezowska, I.; Lemieux, C.; Chung, N. N.; Schiller, P. W. [2',6'-Dimethyltyrosine]dynorphin A(1-11)-$NH_2$ analogues lacking an N-terminal amino group: potent and selective κ opioid antagonists. *J. Med. Chem.* **2001**, *44*, 3048-3053 and references therein.

79. Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Binaltorphimine and nor-binaltorphimine, potent and selective κ-opioid receptor antagonists. *Life Sci.* **1987**, *40*, 1287-1292; Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Bimorphinans as highly selective, potent κ opioid receptor antagonists. *J. Med. Chem.* **1987**, *30*, 238-239.

80. Jewett, D. C.; Woods, J. H. Nor-binaltorphimine: an ultra-long acting kappa-opioid antagonist in pigeons. *Behav. Pharmacol.* **1995**, *6*, 815-820.

81. Takemori, A. E.; Ho, B. Y.; Naeseth, J. S.; Portoghese, P. S. Nor-binaltorphimine, a highly selective *kappa*-opioid antagonist in analgesia and receptor binding assays. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 255-258.

82. Schwyzer, R. ACTH: a short introductory review. *Ann. N. Y. Acad. Sci.* **1977**, *297*, 3-26.

83. Portoghese, P. S.; Nagase, H.; Takemori, A. E. Only one pharmacophore is required for the κ opioid antagonist selectivity of norbinaltorphimine. *J. Med. Chem.* **1988**, *31*, 1344-1347.

84. Jones, R. M.; Hjorth, S. A.; Schwartz, T. W.; Portoghese, P. S. Mutational evidence for a common κ antagonist binding pocket in the wild-type κ and mutant μ[K303E] opioid receptors. *J. Med. Chem.* **1998**, *41*, 4911-4914.

85. Lin, C. -E.; Takemori, A. E.; Portoghese, P. S. Synthesis and κ-opioid antagonist selectivity of a norbinaltorphimine congener. Identification of the address moiety required for κ-antagonist activity. *J. Med. Chem.* **1993**, *36*, 2412-2415.

86. Jales, A. R.; Husbands, S. M.; Lewis, J. W. Selective κ-opioid antagonists related to naltrindole. Effect of side-chain spacer in the 5'-amidinoalkyl series. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2259-2261.

87. Olmsted, S. L.; Takemori, A. E; Portoghese, P. S. A remarkable change of opioid receptor selectivity on the attachment of a peptidomimetic κ address element to the δ antagonist, naltrindole: 5'-[($N^2$-alkylamidino)methyl]naltrindole derivatives as a novel class of κ opioid receptor antagonists. *J. Med. Chem.* **1993**, *36*, 179-180.

88. Stevens, W. C.; Jones, R. M.; Subramanian, G.; Metzger, T. G.; Ferguson, D. M.; Portoghese, P. S. Potent and selective indolomorphinan antagonists of the kappa-opioid receptor. *J. Med. Chem.* **2000**, *43*, 2759-2769 and references therein.

89. Ananthan, S.; Johnson, C. A.; Carter, R. L.; Clayton, K. C.; Rice, K. C.; Xu, H.; Davis, P.; Porreca, F.; Rothman, R. B. Synthesis, opioid receptor binding, and bioassay of naltrindole analogues substituted in the indolic benzene moiety. *J. Med. Chem.* **1988**, *41*, 2872-2881.

90. Thomas, J. B.; Mascarella, S. W.; Rothman, R. B.; Partilla, J. S.; Xu, H.; Mc Cullough, K. B.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F.

I. Investigation of the N-substituent conformation governing potency and μ receptor subtype-selectivity in (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)-piperidine opioid antagonists. *J. Med. Chem.* **1998**, *41*, 1980-1990.

91. Thomas, J. B.; Atkinson, R. N.; Namdev, N.; Rothman, R. B.; Scott, E. F.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y. -F.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of the first *trans*-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)-piperidine derivative to possess highly potent and selective opioid κ receptor antagonist activity. *J. Med. Chem.* **2001**, *44*, 2687-2690.

92. Thomas, J. B.; Fall, M. J.; Cooper, J. B.; Rothman, R. B.; Mascarella, S. W.; Xu, H.; Partilla, J. S.; Dersch, C. M.; Mc Cullough, K. B.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of an opioid κ receptor subtype-selective N-substituent for (+)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)-piperidine. *J. Med. Chem.* **1998**, *41*, 5188-5197.

93. Thomas, J. B.; Atkinson, R. N.; Namdev, N.; Rothman, R. B.; Gigstad, K. M.; Fix, S. E.; Mascarella, S. W.; Burgess, J. P.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Discovery of an opioid κ receptor selective pure antagonist from a library of N-substituted 4β-methyl-5-(3-hydroxyphenyl)morphans. *J. Med. Chem.* **2002**, *45*, 3524-3530.

94. Zimmerman, D. M.; Nickander, R.; Horng, J. S.; Wong, D. T. New structural concepts for narcotic antagonists defined in a 4-phenylpiperidine series. *Nature* **1978**, *275*, 332-334.

95. Thomas, J. B.; Zheng, X.; Mascarella, S. W.; Rothman, R. B.; Dersch, C. M.; Partilla, J. S.; Flippen-Anderson, J. L.; George, C. F.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. N-Substituted 9β-methyl-5-(3-hydroxyphenyl)morphans are opioid receptor pure antagonists. *J. Med. Chem.* **1998**, *41*, 4143-4149.

96. de Costa, B. R.; Rothman, R. B.; Bykov, V.; Jacobson, A. E.; Rice, K. C. Selective and enantiospecific acylation of κ opioid receptors by (1*S*,2*S*)-*trans*-2-isothiocyanato-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide. Demonstration of κ receptor heterogeneity. *J. Med. Chem.* **1989**, *32*, 281-283.

97. Chang, A. -C.; Takemori, A. E.; Portoghese, P. S. 2-(3,4-Dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-(3-isothiocyanatophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide: an opioid receptor affinity label that produces selective and long-lasting κ antagonism in mice. *J. Med. Chem.* **1994**, *37*, 1547-1549.

98. Comer, S. D.; Burke, T. F.; Lewis, J. W.; Woods, J. H. Clocinnamox: a novel, systemically-active, irreversible opioid antagonist. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 1051-1058.

99. Sebastian, A.; Bidlack, J. M.; Jiang, Q.; Deecher, D.; Teitler, M.; Glick, S. D.; Archer, S. 14β-[(*p*-Nitrocinnamoyl)amino]morphinones, 14β-[(*p*-nitrocinnamoyl)amino]-7,8-dihydromorphinones, and their codeinone analogues: synthesis and receptor activity. *J. Med. Chem.* **1993**, *36*, 3154-3160.

100. Korlipara, V. L.; Takemori, A. E.; Portoghese, P. S. *N*-benzylnaltrindoles as long-acting δ-opioid receptor antagonists. *J. Med. Chem.* **1994**, *37*, 1882-1885.

101. Black, S. L.; Chauvignac, C.; Grundt, P.; Miller, C. N.; Howell, S.; Traynor, J. R.; Lewis, J. W.; Husbands S. M. Guanidino N-substituted and N,N-disubstituted derivatives of the κ-opioid antagonist GNTI. *J. Med. Chem.* **2003**, *46*, 5505-5511; Jones, R. M.; Portoghese, P. S. 5'-Guanidinonaltrindole, a highly selective and potent κ-opioid receptor antagonist. *Eur. J. Pharmacol.* **2000**, *396*, 49-52.

102. Portoghese, P. S.; Nagase, H.; Lipkowski, A. W.; Larson, D. L.; Takemori, A. E. Binaltorphimine-related bivalent ligands and their κ opioid receptor antagonist selectivity. *J. Med. Chem.* **1988**, *31*, 836-841.

103. Thomas, J. B.; Atkinson, R. N.; Vinson, N. A.; Catanzaro, J. L.; Perretta, C. L.; Fix, S. E.; Mascarella, S. W.; Rothman, R. B.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Identification of (3*R*)-7-hydroxy-*N*-((1S)-1-[[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide as a novel potent and selective opioid kappa receptor antagonist. *J. Med. Chem.* **2003**, *46*, 3127-3137.

104. Thomas, J. B.; Scott, E. F.; Rothman, R. B.; Mascarella, S. W.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. Importance of phenolic address groups in opioid kappa receptor selective antagonists. *J. Med. Chem.* **2004**, *47*, 1070-1073.

105. Kim, H. -O.; Mathew, F.; Ogbu, C. A convenient synthesis of disubstituted guanidines via the Mitsunobu protocol. *Synlett* **1999**, 193-194.

106. Black, S. L. The design, synthesis and pharmacological evaluation of ligands targeted at the kappa opioid receptor. Thesis submitted to University of Bath, UK, 2001.

107. Williams, I. A. Towards novel short-acting antagonist ligands for the kappa opioid receptor. Transfer report submitted to University of Bath, UK, 2003.

108. Maryanoff, C. A; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. A convenient synthesis of guanidines from thioureas. *J. Org. Chem.* **1986**, *51*, 1882-1884 and references therein.

109. Kämpf, A. Über Darstellung aromatisch substituirter Guanidine aus Cyanamid. *Chem. Ber.* **1904**, *37*, 1681-1684.

110. Arndt, F.; Roseneau, B. Über cyclische Azoxy-Verbindungen. *Chem. Ber.* **1917**, *50*, 1248-1261.

111. Eilingsfeld, H.; Neubauer, G.; Seefelder, M.; Weidinger, H. Synthese und Reaktionen von Chlorformamidiniumchloriden. *Chem. Ber.* **1964**, *97*, 1232-1241.

112. Kim, K.; Lin, Y. -T.; Mosher, H. S. Monosubstituted guanidines from primary amines and aminoiminomethanesulfonic acid. *Tetrahedron Lett.* **1988**, *29*, 3183-3186.

113. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. Diprotected triflylguanidines: a new class of guanidinylation reagents. *J. Org. Chem.* **1998**, *63*, 3804-3805.

114. Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. A mild and efficient method for the preparatioon of guanidines. *Tetrahedron Lett.* **1992**, *33*, 5933-5936.

115. Atwal, K. S.; Ahmed, S. Z.; O'Reilly, B. C. A facile synthesis of cyanoguanidines from thioureas. *Tetrahedron Lett.* **1989**, *30*, 7313-7316.

116. Levallet, C.; Lerpiniere, J.; Ko, S. Y. The $HgCl_2$-promoted guanylation reaction: the scope and limitations. *Tetrahedron* **1997**, *53*, 5291-5304 and references therein.

117. Nicolaou, K. C.; Bunnage, M. E.; Koide, K. Total synthesis of Balanol. *J. Am. Chem. Soc.* **1994**, *116*, 8402-8403.

118. Lange, G. L.; Gottardo, C. Facile conversion of primary and secondary alcohols to alkyl iodides. *Synth. Comm.* **1990**, *20*, 1473-1479.

119. Yoshino, H.; Tsujii, M.; Kodama, M.; Komeda, K.; Niikawa, N.; Tanase, T.; Asakawa, N.; Nose, K.; Yamatsu, K. A large-scale synthesis of [MeTyr$^1$, MeArg$^7$, D-Leu$^8$]Dynorphin A-(1-8)-NHEt (E-2078) by application of the trifluoroacetic acid-pentamethylbenzene deprotecting procedure in the final stage. *Chem. Pharm. Bull.* **1990**, *38*, 1735-1737.

120. Yoshino, H.; Tsuchiya, Y.; Saito, I.; Tsujii, M. Promoting effect of pentamethylbenzene on the deprotection of *O*-benzyltyrosine and $N^{\varepsilon}$-benzyloxycarbonyllysine with trifluoroacetic acid. *Chem. Pharm. Bull.* **1987**, *35*, 3438-3441.

121. Topliss, J. G. A manual method for applying the Hansch approach to drug design. *J. Med. Chem.* **1977**, *20*, 463-469.

122. Portoghese, P. S.; Larson, D. L.; Jiang, J. B.; Takemori, A. E.; Caruso, T. P. 6*β*-[*N*,*N*-Bis(2-chloroethyl)amino]-17-(cyclopropylmethyl)-4,5*α*-epoxy-3,14-dihydroxymorphinan (chloranaltrexamine), a potent opioid receptor alkylating agent with ultralong narcotic antagonist activity. *J. Med. Chem.* **1978**, *21*, 598-599.

123. Portoghese, P. S.; Larson, D. L.; Sayre, L. M.; Fries, D. S. A novel opioid receptor site directed alkylating agent with irreversible narcotic antagonistic and reversible agonistic activities. *J. Med. Chem.* **1980**, *23*, 233-234.

124. Jiang, Q.; Seyed-Mozaffari, A.; Archer, S.; Bidlack, J. M. Antinociceptive properties of two alkylating derivatives of morphinone: 14-β-(thioglycolamido)-7,8-dihydromorphinone (TAMO) and 14-β-(bromoacetamido)-7,8-dihydro-morphinone (H2BAMO). *J. Pharmacol. Exp. Ther.* **1992**, *262*, 526-531.

125. Tsuge, O. The chemistry of cyanates and their thio derivatives. S. Patai ed., pt.1, Wiley, New York, **1977**, *Chapter 13*, 445-453.

126. Frank, R. L.; Smith, P. V. Organic syntheses, **1955**, Coll. Vol *3*, 735-736.

127. March, J. Advanced organic chemistry. 4$^{th}$ Ed., Wiley, New York, **1992**.

128. Boas, U.; Jakobsen, M. H. A new synthesis of aliphatic isothiocyanates from primary amines, convenient for *in-situ* use. *J. Chem. Soc., Chem. Commun.* **1995**, 1995-1996.

129. Barton, D. H. R.; Tachdjian, C. The invention of radical reactions. Part XXVI. New thio- and seleno-hydroxamic acids; radical chemistry of their *O*-acyl derivatives. *Tetrahedron* **1992**, *48*, 7091-7098.

130. Korlipara, V. L.; Takemori, A. E.; Portoghese, P. S. Electrophilic *N*-benzylnaltrindoles as δ opioid receptor-selective antagonists. *J. Med. Chem.* **1995**, *38*, 1337-1343.

131. Kim, S.; Yi, K. Y. Di-2-pyridyl thionocarbonate. A new reagent for the preparation of isothiocyanates and carbodiimides. *Tetrahedron Lett.* **1985**, *26*, 1661-1664.

132. Muller, D.; Zeltser, I.; Bitan, G.; Gilon, C. Building units for N-backbone cyclic peptides. Synthesis of protected $N^{\alpha}$-(ω-aminoalkyl)amino acids and $N^{\alpha}$-(ω-carboxyalkyl)amino acids. *J. Org. Chem.* **1997**, *62*, 411-416.

133. Coates, P. A.; Grundt, P.; Robinson, E. S. J.; Nutt, D. J.; Tyacke, R.; Hudson, A. L.; Lewis, J. W.; Husbands S. M. Probes for imidazoline binding sites: synthesis and evaluation of a selective, irreversible $I_2$ ligand. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 605-607.

134. Schenk, K. J.; Ogle, C. A.; Chapuis, G.; Cavagnat, R.; Jokic, A.; Rey-Lafon, M. A vibrational and structural study of the solid-solid phase transitions in $C_{10}H_{21}NH_3Cl$. *J. Phys. Chem.* **1989**, *93*, 5040-5049.

135. Itsuno, S.; Koizumi, T.; Okumura, C.; Ito, K. Synthesis of primary amines using potassium 1,1,3,3-tetramethyldisilazide as aminating agent of alkyl halides. *Synthesis* **1995**, 150-152.

136. Langenbeck, W.; Woltersdorf, W.; Blachnitzky, H. Die Darstellung des Putrescins aus Butadien. *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 671-672.

137. Gibson, M. S.; Bradshaw, R. W. The Gabriel synthesis of primary amines. *Angew. Chem. internat. Edit.* **1968**, *7*, 919-930.

138. Ing, H. R.; Manske, R. F. H. A modification of the Gabriel synthesis of amines. *J. Chem. Soc.* **1926**, 2348-2351.

139. Li, A. -H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X. -D.; Jacobson, K. A. Synthesis, CoMFA analysis, and receptor docking of 3,5-diacyl-2,4-dialkylpyridine derivatives as selective $A_3$ adenosine receptor antagonists. *J. Med. Chem.* **1999**, *42*, 706-721.

140. Purchase, C. F.; Goel, O. P. A new synthesis of primary aliphatic amines by N-N-didebenzylation. Synthesis of a pirmenol (CI-845) metabolite. *J. Org. Chem.* **1991**, *56*, 457-459.

141. Derrick, I.; Moynihan, H. A.; Broadbear, J. H.; Woods, J. H.; Lewis, J. W. 6N-Cinnamoyl-β-naltrexamine and its *p*-nitro derivative. High efficacy κ-opioid agonists with weak antagonist actions. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 167-172.

142. Ballini, R. New and convenient synthesis of (*Z*)-heneicos-6-en-11-one, the Douglas Fir Tussock Moth (*Orgyia pseudotsugata*) sex pheromone, and (*Z*)-non-6-en-2-one, the immediate precursor for the synthesis of Brevicomin, the sex attractant of the Western pine beetle *Dentroctonus brevicomis*. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1419-1421.

143. Saeed-y-Atto; Potter, A.; Singh, H.; Tedder, J. M. Free radical substitution. The chlorination of 1- and 2-nitrobutanes in the gas and liquid phases. *J. Chem. Soc. Perkin Trans. 2* **1982**, 139-141.

144. Crocker, P. J.; Saha, B.; Ryan, W. J.; Wiley, J. L.; Martin, B. R.; Ross, R. A.; Pertwee, R. G.; Razdan, R. K. Development of agonists, partial agonists and antagonists in the $\Delta^8$-tetrahydrocannabinol series. *Tetrahedron* **1999**, *55*, 13907-13926.

145. Ram, S.; Ehrenkaufer, R. E. A general procedure for mild and rapid reduction of aliphatic and aromatic nitro compounds using ammonium formate as a catalytic hydrogen transfer agent. *Tetrahedron Lett.* **1984**, *25*, 3415-3418 and references therein.

146. Chary, K. P.; Ram, S. R.; Iyengar, D. S. Reductions using $ZrCl_4/NaBH_4$: a novel efficient conversion of aromatic, aliphatic nitro compounds to primary amines. *Synlett* **2000**, 683-685 and references therein.

147. Riebsomer, J. L. Arylsulfonyl esters of nitro alcohols. *J. Org. Chem.* **1946**, *11*, 182-184 and references therein.

148. Durand, G.; Polidori, A.; Salles, J. -P.; Pucci, B. Synthesis of a new family of glycolipidic nitrones as potential antioxidant drugs for neurodegenerative disorders. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 859-862.

149. Chauvignac, C.; Miller, C. N.; Srivastava, S. K.; Lewis, J. W.; Husbands, S. M.; Traynor, J. R. Major effect of pyrrolic N-benzylation in norbinaltorphimine, the selective κ-opioid receptor antagonist. *J. Med. Chem.* **2005**, *48*, 1676-1679.

150. Schmidhammer, H.; Schwarz, P. Unerwartete Reaktion von gemischten Azinen von Dihydrocodeinon mit Methansulfonsäure. *Liebigs Ann. Chem.* **1994**, 445-447.

151. Personal communication from Carroll, F. I.

152. Treibs, A.; Michl, K. -H. Über N-Benzoylpyrrole. *Justus Liebigs Ann.* **1952**, *577*, 115-119; Beach, L.; Batchelor, R. J.; Einstein, F. W. B.; Bennet, A. J. General base-catalyzed hydrolysis and carbonyl-$^{18}O$ exchange of *N*-(4-nitrobenzoyl)pyrrole. *Can. J. Chem.* **1998**, *76*, 1410-1417.

153. Broggini, G.; Casalone, G.; Garanti, L.; Molteni, G.; Pilati, T.; Zecchi, G. Asymmetric induction by the (S)-1-phenylethyl group in intramolecular nitrile

imine cycloadditions giving enantiopure 3,3a-dihydro-pyrazolo[1,5-a][1,4]benzodiazepine-4(6H)-ones. *Tetrahedron: Asymmetry* **1999**, *10*, 4447-4454.

154. Koolpe, G. A.; Nelson, W. L.; Gioannini, T. L.; Angel, L.; Simon, E. J. Diastereomeric 6-desoxy-6-spiro-$\alpha$-methylene-$\gamma$-butyrolactone derivatives of naltrexone and oxymorphone. Selective irreversible inhibition of naltrexone binding in an opioid receptor preparation by a conformationally restricted Michael acceptor ligand. *J. Med. Chem.* **1984**, *27*, 1718-1723.

155. Dasher, W. E.; Klein, P.; Nelson, W. L. Electrophilic opioid ligands. Oxygen tethered $\alpha$-methylene-$\gamma$-lactone, acrylate, isothiocyanate, and epoxide derivatives of 6$\beta$-naltrexol. *J. Med. Chem.* **1992**, *35*, 2374-2384.

156. Nagase, H.; Abe, A.; Portoghese, P. S. The facility of formation of a $\Delta^6$ bond in dihydromorphinone and related opiates. *J. Org. Chem.* **1989**, *54*, 4120-4125.

157. Jr. Chapman, J. M.; Voorstad, P. J.; Cocolas, G. H.; Hall, I. H. Hypolipidemic activity of phthalimide derivatives. 2. *N*-Phenylphthalimide and derivatives. *J. Med. Chem.* **1983**, *26*, 237-243.

158. Tanaka, A.; Oritani, T. A mild and efficient method for converting alcohols and tetrahydropyranyl ethers to bromides with inversion of configuration. *Tetrahedron Lett.* **1997**, *38*, 1955-1956.

159. Aizpurua, J. M.; Cossio, F. P.; Palomo, C. Reaction of hindered trialkylsilyl esters and trialkylsilyl ethers with triphenylphosphine dibromide: preparation of carboxylic acid bromides and alkyl bromides under mild neutral conditions. *J. Org. Chem.* **1986**, *51*, 4941-4943.

160. Costello, C. A.; Kreuzman, A. J.; Zmijewski, M. J. Selective deprotection of phthalylprotected amines. *Tetrahedron Lett.* **1996**, *37*, 7469-7472; Briggs, B. S.; Kreuzman, A. J.; Whitesitt, C.; Yeh, W. -K.; Zmijewski, M. Discovery,

purification, and properties of *o*-phthalyl amidase from *Xanthobacter agilis*. *J. Mol. Catalysis B: Enzymatic 2* **1996**, *34*, 53-69.

161. Fisher, M. J.; Gunn, B.; Harms, C. S.; Kline, A. D.; Mullaney, J. T.; Nunes, A.; Scarborough, R. M.; Arfsten, A. E.; Skelton, M. A.; Um, S. L.; Utterback, B. G.; Jakubowski, J. A. Non-peptide RGD surrogates which mimic a Gly-Asp $\beta$-Turn: potent antagonists of platelet glycoprotein IIb-IIIa. *J. Med. Chem.* **1997**, *40*, 2085-2101.

162. Greene, T. W.; Wuts, P. G. M. Protective groups in organic synthesis. Third Edition, Wiley, New York, **1999**, 127-141.

163. Schmidhammer, H.; Ganglbauer, E.; Mitterdorfer, J.; Rollinger, J. M. 14,14'-Dimethoxy analogues of norbinaltorphimine: synthesis and determination of their κ opioid antagonist selectivity. *Helv. Chim. Acta* **1990**, *73*, 1779-1783 and references therein.

164. Krassnig, R.; Koch, M.; Jennewein, H. K.; Greiner, E.; Schmidhammer, H. A new and efficient synthesis of the μ-opioid receptor antagonists 14-*O*-methyl- and 14-*O*-ethylnaloxone and -naltrexone. *Heterocycles* **1998**, *47*, 1029-1302.

165. Kobylecki, R. J.; Carling, R. W.; Lord, J. A. H.; Smith, C. F. C.; Lane, A. C. Common anionic receptor site hypothesis: its relevance to the antagonist action of naloxone. *J. Med. Chem.* **1982**, *25*, 116-120.

166. Schmidhammer, H.; Schwarz, P.; Wei, Z. -Y. A novel and efficient synthesis of 14-alkoxy-substituted indolo- and benzofuromorphinans in the series of selective δ-opioid receptor antagonists. *Helv. Chim. Acta* **1998**, *81*, 1215-1223.

167. Smith, M.; Rammler, D. H.; Goldberg, I. H.; Khorana, H. G. Studies on polynucleotides. Specific synthesis of the $C_{3'}$-$C_{5'}$ inter-ribonucleotide linkage. Syntheses of uridylyl-(3' → 5')-uridine and uridylyl-(3' → 5')-adenosine. *J. Am. Chem. Soc.* **1962**, *84*, 430-440.

168. Anastasia, L.; Cighetti, G.; Allevi, P. Simple and selective one-pot replacement of the *N*-methyl group of tertiary amines by quaternization and demethylation with sodium sulfide or potassium thioacetate: an application to the synthesis of pergolide. *J. Chem. Soc. Perkin Trans. 1* **2001**, 2398-2403 and references therein.

169. Weiss, U. Derivatives of morphine. 14-Hydroxydihydromorphinone. *J. Am. Chem. Soc.* **1955**, *77*, 5891-5892.

170. Weiss, U. Derivatives of morphine. Demethylation of 14-hydroxycodeinone, 14-hydroxymorphinone and 8,14-dihydroxydihydromorphinone. *J. Org. Chem.* **1957**, *22*, 1505-1508.

171. Iijima, I.; Minamikawa, J. -I.; Jacobson, A. E.; Brossi, A.; Rice, K. C. Studies in the (+)-morphinan series. Synthesis and biological properties of (+)-naloxone. *J. Med. Chem.* **1978**, *21*, 398-400.

172. Williard, P. G.; Fryhle, C. B. Boron trihalide-methyl sulfide complexes as convenient reagents for dealkylation of aryl ethers. *Tetrahedron Lett.* **1980**, *21*, 3731-3734.

173. Lipkowski, A. W.; Nagase, H.; Portoghese, P. S. A novel pyrrole synthesis via reaction of ketones with N-aminoimides. *Tetrahedron Lett.* **1986**, *27*, 4257-4260.

174. Schmidhammer, H.; Smith, C. F. C. A simple and efficient method for the preparation of binaltorphimine and derivatives and determination of their κ opioid antagonist selectivity. *Helv. Chim. Acta* **1989**, *72*, 675-677.

175. Mestres, R.; Palenzuela, J. High atomic yield bromine-less benzylic bromination. *Green Chem.* **2002**, *4*, 314-316.

176. Kikuchi, D.; Sakaguchi, S.; Ishii, Y. An alternative method for the selective bromination of alkylbenzenes using $NaBrO_3/NaHSO_3$ reagent. *J. Org. Chem.* **1998**, *63*, 6023-6026.

177. Cheng, Y. -C.; Prusoff, W. H. Relationship between the inhibition constant ($K_i$) and the concentration of inhibitor which causes 50 per cent inhibition ($I_{50}$) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108. Chou, T. C. Relationships between inhibition constants and fractional inhibition in enzyme-catalyzed reactions with different numbers of reactants, different reaction mechanisms, and different types and mechanisms of inhibition. *Mol. Pharmacol.* **1974**, *10*, 235-247.

178. Broom, D. C.; Guo, L.; Coop, A.; Husbands, S. M.; Lewis, J. W.; Woods, J. H.; Traynor, J. R. BU48 : A novel buprenorphine analogue that exhibits delta-opioid mediated convulsions but not delta-opioid mediated antinociception in mice. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 1195-1200.

179. Traynor, J. R.; Nahorski, S. R. Modulation by mu-opioid agonists of guanosine-5'-O-(3-[S-35]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. *Mol. Pharmacol.* **1995**, *47*, 848-854.

180. Broadbear, J. H.; Sumpter, T. L.; Burke, T. F.; Husbands, S. M.; Lewis, J. W.; Woods, J. H.; Traynor, J. R. Methocinnamox is a potent, long-lasting and selective antagonist of morphine-mediated antinociception in the mouse: comparison with clocinnamox, $\beta$-FNA and $\beta$-chlornaltrexamine. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 933-940.

181. Portoghese, P. S.; Larson, D. L.; Sultana, M.; Takemori, A. E. Opioid agonist and antagonist activities of morphindoles related to naltrindole. *J. Med. Chem.* **1992**, *35*, 4325-4329.

182. Nieland, N. Investigations of derivatives of 14$\beta$-amino-7,8-dihydromorphinone. Thesis submitted to University of Bristol, UK, 2001.

183. McLaughlin, J. P.; Hill, K. P.; Jiang, Q.; Sebastian, A.; Archer, S.; Bidlack, J. M. Nitrocinnamoyl and chlorocinnamoyl derivatives of dihydrocodeinone: in vivo and in vitro characterization of μ-selective agonist and antagonist activity. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 304-311.

183a Portoghese, P. S.; Sultana, M.; Takemori, A. E. Design of peptidomimetic δ opioid receptor antagonists using the message-address concept. *J. Med. Chem.* **1990**, *33*, 1714-1720.

184. Chow, H. -F.; Mak, C. C. Dendritic bis(oxazoline)copper(II) catalysts. Synthesis, reactivity, and substrate selectivity. *J. Org. Chem.* **1997**, *62*, 5116-5127 and references therein.

185. Brun, K. A.; Linden, A.; Heimgartner, H. New optically active 2*H*-azirin-3-amines as synthons for enantiomerically pure 2,2-disubstituted glycines: synthesis of synthons for Tyr(2Me) and Dopa(2Me), and their incorporation into dipeptides. *Helv. Chim. Acta* **2002**, *85*, 3422-3443.

186. Bender, D. M.; Williams, R. M. An efficient synthesis of (*S*)-*m*-tyrosine. *J. Org. Chem.* **1997**, *62*, 6690-6691.

187. Kurosawa, W.; Kan, T.; Fukuyama, T. Stereocontrolled total synthesis of (–)-ephedradine A (Orantine). *J. Am. Chem. Soc.* **2003**, *125*, 8112-8113.

188. Chang, C. -Y.; Kuo, S. -C.; Lin, Y. -L.; Wang, J. -P.; Huang, L. -J. Benzyloxybenzaldehyde analogues as novel adenylyl cyclase activators. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1971-1974.

189. Zwaagstra, M. E.; Timmerman, H.; Tamura, M.; Tohma, T.; Wada, Y.; Onogi, K.; Zhang, M. -Q. Synthesis and structure-activity relationships of carboxylated chalcones: a novel series of *CysLT*$_1$ ($LTD_4$) receptor antagonists. *J. Med. Chem.* **1997**, *40*, 1075-1089.

190. Ōki, M.; Iwamura, H. Intramolecular interaction between hydroxyl group and π-electrons. Electronic effect in arylcarbinols and a preliminary note on the interaction in benzylaniline derivatives. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 955-959.

191. Thakkar, K.; Geahlen, R. L.; Cushman, M. Synthesis and protein-tyrosine kinase inhibitory activity of polyhydroxylated stilbene analogues of piceatannol. *J. Med. Chem.* **1993**, *36*, 2950-2955 and references therein.

192. Ali, M. H.; Wiggin, C. J. Silica gel supported Jones reagent (SJR): A simple and efficient reagent for oxidation of benzyl alcohols to benzaldehydes. *Synth. Commun.* **2001**, *31*, 1389-1398.

193. Brown, H. C.; Narasimhan, S.; Choi, Y. M. Selective reductions. Effect of cation and solvent on the reactivity of saline borohydrides for reduction of carboxylic esters. Improved procedures for the conversion of esters to alcohols by metal borohydrides. *J. Org. Chem.* **1982**, *47*, 4702-4708.

194. Shapiro, M. J. π-Inductive effects in benzyl compounds. *J. Org. Chem.* **1977**, *42*, 762-763.

195. Yoh, S. -D., Cheong, D. -Y.; Lee, C. -H.; Kim, S. -H.; Park, J. -H.; Fujio, M.; Tsuno, Y. Concurrent $S_N1$ and $S_N2$ reactions in the benzylation of pyridines. *J. Phys. Org. Chem.* **2001**, *14*, 123-130.

196. Linney, I. D.; Buck, I. M.; Harper, E. A.; Kalindjian, S. B.; Pether, M. J.; Shankley, N. P.; Watt, G. F.; Wright, P. T. Design, synthesis, and structure-activity relationships of novel non-imidazole histamine $H_3$ receptor antagonists. *J. Med. Chem.* **2000**, *43*, 2362-2370.

197. Pittelkow, M.; Lewinsky, R.; Christensen, J. B. Selective synthesis of carbamate protected polyamines using alkyl phenyl carbonates. *Synthesis* **2002**, 2195-2202.

198. Hanaoka, K.; Kikuchi, K.; Urano, Y.; Nagano, T. Selective sensing of zinc ions with a novel magnetic resonance imaging contrast agent. *J. Chem. Soc. Perkin Trans. 2* **2001**, 1840-1843.

199. Kneeland, D. M.; Ariga, K.; Lynch, V. M.; Huang, C. -Y.; Anslyn, E. V. Bis(alkylguanidinium) receptors for phosphodiesters: effect of counterions, solvent mixtures, and cavity flexibility on complexation. *J. Am. Chem. Soc.* **1993**, *115*, 10042-10055.

200. McWatt, M.; Boons, G. -J. Parallel combinatorial synthesis of glycodendrimers and their hydrogelation properties. *Eur. J. Org. Chem.* **2001**, *13*, 2535-2545.

201. Ulhaq, S.; Chinje, E. C.; Naylor, M. A.; Jaffar, M.; Stratford, I. J.; Threadgill, M. D. Heterocyclic analogues of L-citrulline as inhibitors of the isoforms of nitric oxide synthase (NOS) and identification of $N^{\delta}$-(4,5-dihydrothiazol-2-yl)ornithine as a potent inhibitor. *Bioorg. Med. Chem.* **1999**, *7*, 1787-1796.

202. Davis, A. L.; Skinner, C. G.; Shive, W. The conformation of lysine on its site of biological utilization. *J. Am. Chem. Soc.* **1961**, *83*, 2279-2281.

203. Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. Free radical-mediated vinyl amination: a mild, general pyrrolidinyl enamine synthesis. *Tetrahedron* **2003**, *59*, 8877-8888.

204. Prabhakaran, P. C.; Gould, S. J.; Orr, G. R.; Coward, J. K. Synthesis of chirally deuteriated phthalimidopropanols and evaluation of their absolute stereochemistry. *J. Am. Chem. Soc.* **1988**, *110*, 5779-5784.

205. Martinkus, K. J.; Tann, C. -H.; Gould, C. J. The biosynthesis of the streptolidine moiety in streptothricin F. *Tetrahedron* **1983**, *39*, 3493-3505.

206. Meguro, M.; Asao, N.; Yamamoto, Y. Ytterbium triflate and high pressure-mediated ring opening of epoxides with amines. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2597-2601.

207. Bigge, C. F.; Johnson, G.; Ortwine, D. F.; Drummond, J. T.; Retz, D. M.; Brahce, L. J.; Coughenour, L. L.; Marcoux, F. W.; Probert, A. W., Jr. Exploration of *N*-phosphonoalkyl-, *N*-phosphonoalkenyl-, and *N*-(phosphonoalkyl)phenyl-spaced $\alpha$-amino acids as competitive *N*-methyl-D-aspartic acid antagonists. *J. Med. Chem.* **1992**, *35*, 1371-1384.

208. Niculescu-Duvaz, D.; Niculescu-Duvaz, I.; Friedlos, F.; Martin, J.; Spooner, R.; Davies, L.; Marais, R.; Springer, C. J. Self-immolative nitrogen mustard prodrugs for suicide gene therapy. *J. Med. Chem.* **1998**, *41*, 5297-5309.

209. de Groot, F. M. H.; Loos, W. J.; Koekkoek, R.; van Berkom, L. W. A.; Busscher, G. F.; Seelen, A. E.; Albrecht, C.; de Bruijn, P.; Scheeren, H. W. Elongated multiple electronic cascade and cyclization spacer systems in activatible anticancer prodrugs for enhanced drug release. *J. Org. Chem.* **2001**, *66*, 8815-8830.

210. Luo, C.; Guldi, D. M.; Imahori, H.; Tamaki, K.; Sakata, Y. Sequential energy and electron transfer in an artificial reaction center: formation of a long-lived charge-separated state. *J. Am. Chem. Soc.* **2000**, *122*, 6535-6551.

211. Li, X.; Chin, D. N.; Whitesides, G. M. Synthesis and evaluation of thioether-based tris-melamines as components of self-assembled aggregates based on the CA·M Lattice. *J. Org. Chem.* **1996**, *61*, 1779-1786.

212. Just, G.; Zamboni, R. β-Lactams. II. The synthesis of *cis*-*N*-(2'-carboxyphenyl)-3-*N*-phenylacetamido-4-methoxymethyl-2-azetidinone. *Can. J. Chem.* **1978**, *56*, 2720-2724.

213. Eguchi, S.; Takeuchi, H. The reactivity of imide carbonyl groups in the intramolecular aza-Wittig reaction. An efficient route to iminolactam derivatives. *J. Chem. Soc., Chem. Commun.* **1989**, 602-603.

214. Rapoport, H.; Naumann, R.; Bissell, E. R.; Bonner, R. M. The preparation of some dihydro ketones in the morphine series by Oppenauer oxidation. *J. Org. Chem.* **1950**, *15*, 1103-1105.

215. Kolb, V. M.; Hua, D. H. Syn-anti isomerism in the opiate hydrazones and azines derived from naloxone, naltrexone and oxymorphone. *J. Org. Chem.* **1984**, *49*, 3824-3828.

216. López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. New synthetic applications of aryllead triacetates. N-Arylation of amides. *J. Org. Chem.* **1996**, *61*, 5865-5870.

# 6.

# ANNEXE

# -

# PUBLICATIONS

# Guanidino N-Substituted and N,N-Disubstituted Derivatives of the κ-Opioid Antagonist GNTI

Shannon L. Black,† Cedric Chauvignac,† Peter Grundt,† Carl N. Miller,‡ Susan Wood,‡ John R. Traynor,‡ John W. Lewis,† and Stephen M. Husbands*,†

*Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK, and Department of Pharmacology, University of Michigan, Ann Arbor, Michigan 48109*

*Received June 10, 2003*

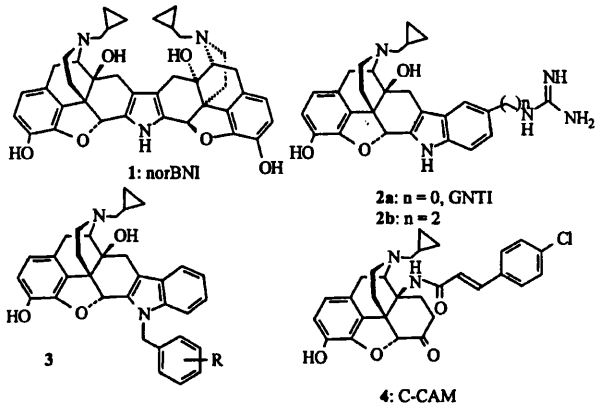
Derivatives of the highly selective κ-opioid receptor antagonist GNTI (**2a**) have been prepared. Binding and functional studies conducted on cloned human opioid receptors expressed in Chinese hamster ovarian (CHO) cells suggested that adding a benzyl or a substituted benzyl group to the guanidino moiety led, in general, to a retention of high κ-affinity and antagonist potency. Disubstitution of the guanidino moiety led to reduced κ-selectivity.

## Introduction

One of the principal goals for medicinal chemists within the field of drug abuse, and in particular opioid abuse, has been the development of selective antagonists for each of the opioid receptors (μ, κ, and δ). The availability of such agents greatly facilitates the study of the physiological function of these receptors. Though the role of opioids in the treatment of pain has long been recognized, it has become increasingly apparent that they have a significant role to play in a wider range of clinical situations and thus there is a continuing need for the development of selective ligands, both as tools for basic research and as leads for potential pharmacotherapies. Of the three opioid receptor types, the μ-receptor has been the most thoroughly investigated due to its involvement in the treatment of pain and opiate abuse. It is, however, becoming increasingly apparent that both the κ- and δ-receptors represent viable molecular targets for a number of indications. Of particular interest to ourselves are reports on the role of κ-opioid agonists in cocaine abuse, and in particular, the findings that κ-agonists can block many of cocaine's behavioral effects.[1–6] Thus κ-agonists may be of use in the development of a treatment for cocaine abuse.

κ-Antagonists have also been studied in the preclinical setting with reports of their utility in improving recovery after traumatic brain injury in rats,[7] for determining the underlying mechanisms that cause the motor fluctuations that develop during the treatment of Parkinson's disease,[8] and as antidepressants in the forced swim test in rats.[9] In feeding studies, administration of the κ-antagonist norBNI (**1**) significantly reduced deprivation intake and suppressed other forms of food intake in rats[10] and has also been shown to attenuate drinking in genetically polydipsic mice.[11]

At present, norBNI, discovered by Portoghese and coworkers, is the κ-antagonist of choice.[12–14] Extensive investigation of the structural requirements for κ-antagonist selectivity has led to GNTI (**2a**), a simplified

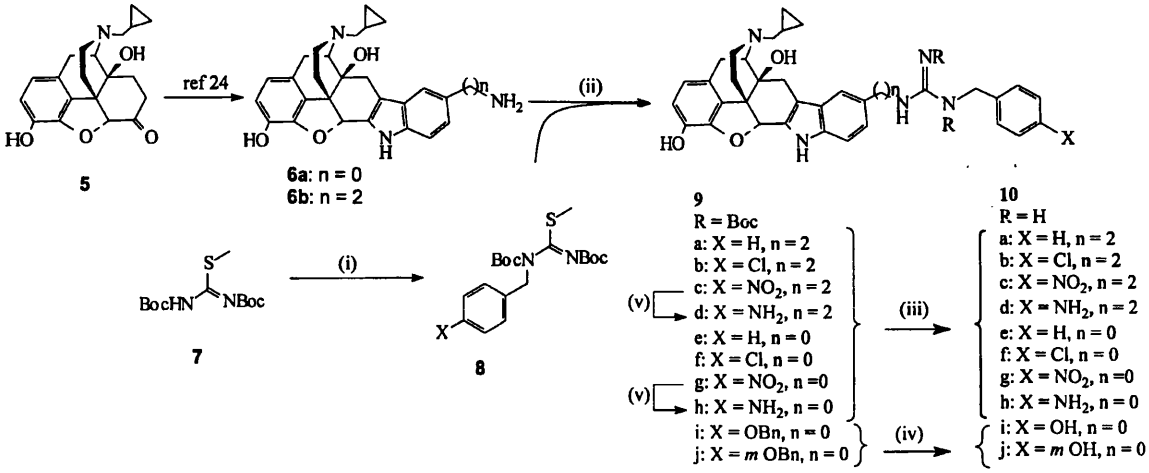



structure based on the indolomorphinan naltrindole.[15,16] Initial reports suggest that **2a** has comparable, or better, κ-antagonist selectivity than **1**[15,16] and shares with **1** an extended duration of action.[17] We were interested in the possibilities that the guanidine group provided for further structural elaboration. Introduction of a lipophilic group into the side chain of μ- and δ-opioid antagonists can have a profound effect on the selectivity, efficacy, and reversibility of the ligands. For example, introduction of arylalkyl groups to the 14-position in a series of δ-antagonists related to naltrindole resulted in a μ-agonist/low-efficacy δ-partial agonist profile.[18] In addition, the indole *N*-benzyl derivative of naltrindole, BNTI (**3**, R = H),[19,20] has no means of forming a covalent bond to the receptor and yet is reported to have an in vivo profile very similar to that of the isothiocyanate-containing BNTII (**3**, R = p-NCS), with antagonist effects lasting up to 5 days. A similar effect has been observed with the well-known μ-receptor irreversible antagonist C-CAM (**4**).[21–23] The available evidence does not suggest that **4** forms a covalent bond with the receptor, yet it displays a pharmacological profile consistent with nonsurmountable binding to the receptor. Presumably, in these cases noncompetitive binding is a result of extremely tight binding involving the benzyl and cinnamoyl groups. If such an effect were replicated in the GNTI (**2a**) series at the κ-receptor, it would result in the first nonsurmountable κ-antagonist based on a

* Corresponding author. Tel: (1225) 383103. Fax: (1225) 386114. E-mail: S.M.Husbands@bath.ac.uk.
† University of Bath.
‡ University of Michigan.

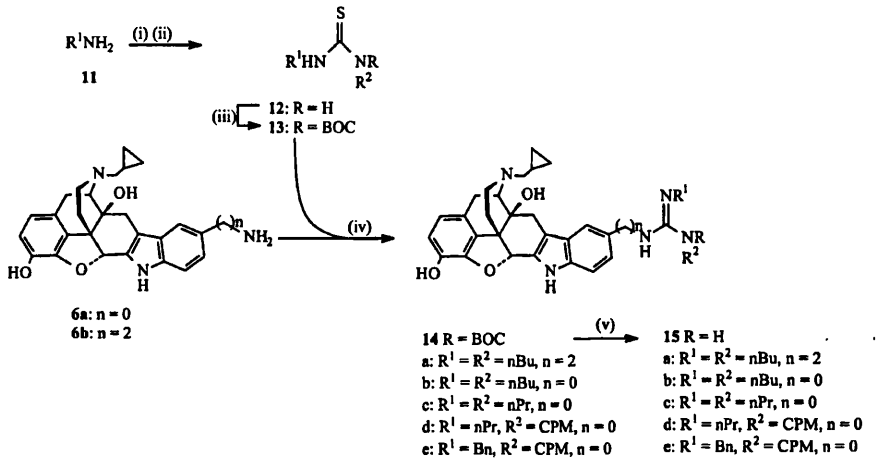
10.1021/jm0309203 CCC: $25.00 
Published on Web 11/12/2003

**Scheme 1**[a]




[a] (i) NaH, X-$C_6H_4CH_2Br$, DMF; (ii) $HgCl_2$, $NEt_3$, DMF; (iii) TFA/$CH_2Cl_2$; (iv) HCl/MeOH; (v) Raney Ni/cyclohexene.

**Scheme 2**[a]




[a] (i) $Cl_2CS$, $CaCO_3$, $H_2O$; (ii) $RNH_2$, acetone; (iii) NaH, $(BOC)_2O$, THF; (iv) $HgCl_2$, $NEt_3$, DMF; (v) TFA, $CH_2Cl_2$.

κ-antagonist, and not κ-agonist, structure. For these reasons benzyl-substituted analogues of **2** were targeted along with a small number of disubstituted aliphatic analogues to extend the SAR.

## Chemistry

The synthesis of guanidines **2a** and **2b** has been previously reported by Stevens et al.[24] They were obtained by mercury-assisted condensation of amines **6a,b** with bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. To access the related *N*-benzyl guanidines it was decided to utilize *N,N'*-bis(*tert*-butoxycarbonyl)-*N*-benzyl-2-methylthiopseudourea and substituted benzyl analogues (**8**), in an analogous reaction. The guanidinylating agents (**8**) were prepared by reaction of the appropriately substituted benzyl bromide with 1,3-bis-(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**7**) in the presence of sodium hydride. Coupling with amine **6b**, to give **9a–c**, was carried out at 50 °C in the presence of mercuric chloride, with the less reactive aniline **6a** requiring extended reaction time at 60 °C to yield **9e–g**. Removal of the *tert*-butoxycarbonyl protecting group was accomplished using standard conditions of trifluoroacetic acid to give the products (**10a–c,e–g**) as their trifluoroacetic acid salts. The nitro analogues **9c,g** were also converted to their amino counterparts **9d,h** by Raney Ni catalyzed transfer hydrogenation in 50% MeOH/cyclohexene before removal of the protecting groups with trifluoroacetic acid to yield **10d,h**.

The *p*- and *m*-hydroxy analogues (**10i,j**) were prepared in similar fashion (Scheme 1), the appropriate guanidinylating agents being synthesized from the *m*- and *p*-benzyloxybenzyl bromides reported previously.[25,26] Simultaneous removal of the *tert*-butoxycarbonyl and benzyl protecting groups of **10i** and **10j** was found to proceed most efficiently in HCl/MeOH to give **10i** and **10j** as their hydrochloride salts.

Disubstituted thioureas **15** were prepared by coupling of **6a** and **6b** with symmetric and unsymmetric *N,N'*-disubstituted thioureas (**13**), themselves prepared from the appropriate amines and thiophosgene (Scheme 2). The coupling would not take place directly with thioureas (**12**), in agreement with literature precedent,[27] and required the presence of a *tert*-butoxycarbonyl group on one of the nitrogens. Interestingly, in the same report[27] it is suggested that the thiourea group should have one proton on each of the nitrogens in order for the coupling reaction to be successful. This does not

**Table 1.** Antagonist Potency in [$^{35}$S]GTPγS Assays Performed in Cloned Human Opioid Receptors[a]

| | | | | $K_e$ (nM) ± SEM | | | | |
|---|---|---|---|---|---|---|---|---|
| compd | *n* | R1 | R2 | μ-CHO membranes DAMGO | δ-CHO membranes DPDPE | κ-CHO membranes U69,593 | μ/κ | δ/κ |
| **2b** | 2 | H | H | 1.25 ± 0.12 | 0.88 ± 0.15 | 0.40 ± 0.06 | 3 | 2 |
| **10a** | 2 | H | benzyl | 2.94 ± 0.31 | 1.36 ± 0.10 | 0.13 ± 0.01 | 23 | 10 |
| **10b** | 2 | H | *p*-chlorobenzyl | 2.61 ± 0.41 | 1.48 ± 0.14 | 0.23 ± 0.02 | 11 | 6 |
| **10c** | 2 | H | *p*-nitrobenzyl | 2.20 ± 0.60 | 1.34 ± 0.24 | 0.17 ± 0.01 | 13 | 8 |
| **10d** | 2 | H | *p*-aminobenzyl | 1.57 ± 0.13 | 0.95 ± 0.14 | 0.25 ± 0.03 | 6 | 4 |
| **10e** | 0 | H | benzyl | 1.41 ± 0.17 | 4.09 ± 0.63 | 0.06 ± 0.01 | 24 | 68 |
| **10f** | 0 | H | *p*-chlorobenzyl | 5.24 ± 1.13 | 7.67 ± 1.36 | 0.14 ± 0.01 | 37 | 55 |
| **10g** | 0 | H | *p*-nitrobenzyl | 3.71 ± 0.59 | 16.66 ± 1.30 | 0.18 ± 0.01 | 21 | 93 |
| **10h** | 0 | H | *p*-aminobenzyl | 1.22 ± 0.06 | 10.80 ± 0.80 | 0.09 ± 0.01 | 14 | 120 |
| **10i** | 0 | H | *p*-hydroxybenzyl | 12.66 ± 0.84 | 18.31 ± 0.95 | 0.10 ± 0.01 | 127 | 183 |
| **10j** | 0 | H | *m*-hydroxybenzyl | 4.28 ± 0.52 | 4.35 ± 0.22 | 0.13 ± 0.02 | 33 | 33 |
| **15a** | 2 | butyl | butyl | 4.62 ± 0.59 | 1.05 ± 0.08 | 0.39 ± 0.03 | 12 | 3 |
| **15b** | 0 | butyl | butyl | 5.66 ± 0.39 | 5.24 ± 0.67 | 0.44 ± 0.03 | 13 | 12 |
| **15c** | 0 | propyl | propyl | 4.59 ± 0.80 | 2.43 ± 0.31 | 0.26 ± 0.05 | 18 | 9 |
| **15d** | 0 | propyl | cyclopropylmethyl | 3.26 ± 0.32 | 6.31 ± 0.34 | 0.08 ± 0.01 | 41 | 79 |
| **15e** | 0 | benzyl | cyclopropylmethyl | 2.75 ± 0.24 | 3.28 ± 0.37 | 0.17 ± 0.05 | 16 | 19 |
| **1** | norBNI | | | 18.9 ± 1.8 | 4.42 ± 0.38 | 0.04 ± 0.004 | 484 | 113 |
| **2a**[b] | GNTI | H | H | 3.23 | 15.49 | 0.04 | 81 | 389 |

[a] Values are means from five or six experiments. [b] Converted from $pA_2$ values from ref 16.

**Table 2.** Binding Affinities to Cloned Human Opioid Receptors Transfected into Chinese Hamster Ovary (CHO) Cells[a]

| | | | | $K_i$ (nM) ± SEM | | | | |
|---|---|---|---|---|---|---|---|---|
| compd | *n* | R1 | R2 | μ [$^3$H]-DAMGO | δ [$^3$H]Cl-DPDPE | κ [$^3$H]U69,593 | μ/κ | δ/κ |
| **2b** | 2 | H | H | 5.69 ± 1.28 | 4.93 ± 1.28 | 0.49 ± 0.00 | 12 | 10 |
| **10a** | 2 | H | benzyl | 3.54 ± 0.25 | 7.24 ± 0.86 | 1.42 ± 0.17 | 2 | 5 |
| **10b** | 2 | H | *p*-chlorobenzyl | 7.74 ± 1.98 | 19.18 ± 0.17 | 2.41 ± 0.22 | 3 | 8 |
| **10c** | 2 | H | *p*-nitrobenzyl | 9.21 ± 3.73 | 11.70 ± 0.28 | 2.14 ± 0.34 | 4 | 5 |
| **10d** | 2 | H | *p*-aminobenzyl | 7.78 ± 2.71 | 5.05 ± 0.23 | 0.95 ± 0.04 | 8 | 5 |
| **10e** | 0 | H | benzyl | 10.47 ± 1.87 | 26.81 ± 6.47 | 0.86 ± 0.20 | 12 | 31 |
| **10f** | 0 | H | *p*-chlorobenzyl | 29.78 ± 0.50 | 85.05 ± 5.06 | 0.66 ± 0.05 | 45 | 129 |
| **10g** | 0 | H | *p*-nitrobenzyl | 26.28 ± 3.82 | 95.82 ± 3.49 | 1.61 ± 0.45 | 16 | 60 |
| **10h** | 0 | H | *p*-aminobenzyl | 7.89 ± 2.45 | 23.91 ± 5.69 | 0.63 ± 0.10 | 13 | 38 |
| **10i** | 0 | H | *p*-hydroxybenzyl | 14.67 ± 3.65 | 41.86 ± 0.93 | 3.26 ± 0.12 | 4.5 | 13 |
| **10j** | 0 | H | *m*-hydroxybenzyl | 14.16 ± 4.11 | 17.58 ± 0.29 | 2.74 ± 0.74 | 5 | 6 |
| **15a** | 2 | butyl | butyl | 7.89 ± 0.57 | 6.73 ± 1.80 | 4.80 ± 0.02 | 1.5 | 1.5 |
| **15b** | 0 | butyl | butyl | 18.27 ± 0.34 | 15.04 ± 3.26 | 6.96 ± 0.85 | 3 | 2 |
| **15c** | 0 | propyl | propyl | 9.83 ± 0.09 | 8.52 ± 1.99 | 2.72 ± 0.39 | 4 | 3 |
| **15d** | 0 | propyl | cyclopropylmethyl | 22.44 ± 7.27 | 15.48 ± 3.47 | 2.38 ± 0.37 | 9 | 6.5 |
| **15e** | 0 | benzyl | cyclopropylmethyl | 17.73 ± 0.30 | 18.06 ± 1.72 | 3.91 ± 0.60 | 4.5 | 5 |
| **1** | norBNI | | | 21.0 ± 5.0 | 5.7 ± 0.9 | 0.20 ± 0.05 | 105 | 28 |
| **2a**[b] | GNTI | H | H | 36.9 ± 2.3 | 70.0 ± 0.3 | 0.18 ± 0.10 | 205 | 389 |

[a] Data are the average from two experiments, each carried out in triplicate. [b] Data from ref 16.

appear to be the case in the current work and may argue against formation of the previously proposed carbodiimide intermediate in these instances.[27]

## Results and Discussion

Opioid agonist and antagonist activity was determined using the [$^{35}$S]GTPγS assay in cloned human opioid receptors transfected into Chinese hamster ovary (CHO) cells (Table 1).[28,29] None of the compounds stimulated [$^{35}$S]GTPγS binding for any type of opioid receptor but were found to be antagonists of the selective agonists DAMGO (μ), Cl-DPDPE (δ), and U69,593 (κ) (Table 1). The ligands were also evaluated in competition binding assays in CHO cells transfected with cloned human opioid receptors (Table 2).[29] The displaced radioligands were [$^3$H]DAMGO (μ), [$^3$H]Cl-DPDPE (δ), and [$^3$H]U69,593 (κ).

Each of the compounds was found to be a potent κ-antagonist with varying selectivity over the μ- and δ-receptors (Table 1). κ-Antagonist potency was consistent throughout the series with little variation between compounds ($K_e$ = 0.06–0.44 nM). Those ligands lacking the ethylene spacer group were consistently more selective for the κ-receptor than those with the spacer group **10e–h** vs **10a–d** and **15a** vs **15b**. This effect was particularly prominent for κ/δ-selectivity but less so for κ/μ. This appears to confirm earlier reports suggesting that in the majority of cases a spacer group was not beneficial for κ-selectivity.[24] In neither series (*n* = 0, 2) was there any evidence of consistent effects of the substituents on the benzyl ring, with the unsubstituted, *p*-amino, *p*-nitro, *p*-chloro, and *m*-hydroxy all having similar κ-antagonist potency and selectivity. The one compound that stood out was **10i**, having a *p*-hydroxy substituent. While **10i** retained antagonist potency at κ-receptors, it was less potent than the other ligands at δ- and μ-receptors, leading to increased κ-selectivity (183-fold over δ and 127-fold over μ). These results are intriguing as the *p*-hydroxy group of **10i** can exactly overlay the second phenolic group of norBNI (**1**) and thus may be interacting unfavorably with the same site/residues on the μ- and δ-receptors. While GNTI (**2a**) was

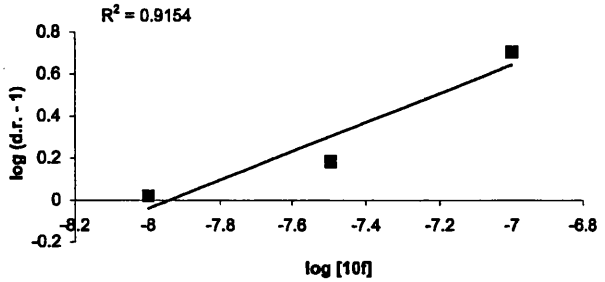



**Figure 1.** Schild plot of the $\kappa$-antagonist activity of **10f**.

not evaluated in this current study, data from the same source and using the same assays as in the present study have been reported previously. Thus, some comparison can be made between **2a** and the current series of compounds with reasonable confidence. **10i** appears similar to both **1** and **2a** in these assays. Of the three, **1** is the most selective for $\kappa/\mu$, but the least selective for $\kappa/\delta$. **2a** is the opposite, with the greatest selectivity over $\delta$ and the least over $\mu$, while **10i** displays a balance, with good selectivity over both $\delta$ and $\mu$ receptors.

The dialkylguanidines (**15a–e**) were again selective antagonists for the $\kappa$-receptor, but in general with somewhat reduced selectivity as compared to the benzyl guanidines (Table 1). The most direct comparison is between **10e**, having a benzyl group, and **15e**, having benzyl and cyclopropylmethyl groups. **10e** showed higher selectivity, particularly with respect to $\kappa/\delta$. That **15d** also displayed higher selectivity than **15e** suggests that the increase in steric bulk on having both cyclopropylmethyl and benzyl groups is detrimental for selectivity. This is a result of slightly reduced $\kappa$-antagonist potency and slightly increased $\mu$- and $\delta$-antagonist potencies for **15e** compared to **15d**.

In the binding assays, all of the ligands bound with highest affinity at the $\kappa$ receptor (Table 2) with Hill slopes approximating unity, indicating competitive binding. Selectivity varied considerably, but with the broad trends comparable to those noted in the functional assay. Thus, benzyl guanidines **10a–d** had substantially lower $\kappa$-selectivity than their analogues **10e–h**; this was particularly evident for $\kappa/\delta$ selectivity. There again appears to be no consistent SAR relating to the ring substituent within this series. Whereas in the functional assays **10i** was most selective, in the binding assays it was the *p*-chloro analogue **10f**. GNTI (**2a**) and its benzyl analogues ($n = 0$) each had higher selectivity for $\kappa/\delta$ than $\kappa/\mu$, whereas, as found in the functional assays, norBNI (**1**) was more selective for $\kappa/\mu$ than $\kappa/\delta$.

The difference between the disubstituted guanidines (**15a–e**) and the monosubstituted benzyl guanidines was even more pronounced in the binding assays than in the functional assays, with **15a–e** displaying little or no $\kappa$-selectivity against the other two opioid receptors.

In the [$^{35}$S]GTP$\gamma$S assays, while the ligands caused a shift in the agonist dose–response curves, there was no indication of flattening of the dose–response curve that would be expected if the compounds were acting in a nonsurmountable manner. However, in C6($\delta$) and CHO($\kappa$), but not C6($\mu$) cells, the compounds tended to display wash-resistant binding that could be indicative of pseudo-irreversibility (data not shown). As norBNI (**1**) also displayed similar binding characteristics in these cell lines, it was felt that further studies in the mouse vas deferens (mvd) would provide a more accurate assessment of their reversibility. To this end, two compounds, **10b** and **10f**, were evaluated for $\kappa$-antagonist activity in the mvd. Both compounds produced surmountable antagonism and parallel shifts of the dose–response curve for the selective $\kappa$-agonist E2078.[30] For **10f** the antagonism was studied in more detail, and the effects were found to be dose-dependent. A Schild plot of the antagonist activity of **10f** indicates a linear relationship with a slope approximating unity (0.7), again indicating competitive binding characteristics (Figure 1). It was noted that the $K_e$ of 20 nM obtained in this mvd assay is considerably higher than the value suggested by the binding and GTP$\gamma$S data.

## Conclusions

The addition of benzyl and substituted-benzyl groups to the guanidino moiety of GNTI (**2a**) results in ligands that retain high affinity and selectivity for the $\kappa$-opioid receptor. Disubstituted guanidines displayed reduced selectivity compared to their monosubstituted counterparts, primarily as a result of lower $\kappa$-affinity. That the benzyl group of these ligands may interact with the same site on the receptor as the second phenolic group of norBNI (**1**) seemed to be confirmed by the substantial selectivity displayed by the *p*-hydroxy analogue (**10i**) in the functional assays. The discrepancy between wash-resistant binding in the C6($\delta$) and CHO($\kappa$) cell lines, yet fully reversible binding in the mvd, may suggest that wash-resistance is not a suitable definition of irreversibility.

## Experimental Section

Column chromatography was performed under gravity, over silica gel 60 (35–70 $\mu$m) purchased from Merck. Preparative TLC was performed on plates made with Kieselgel 60 $PF_{254+366}$ for preparative TLC, obtained from Merck. The thickness of the silica layer was approximately 1 mm. Analytical TLC was performed using aluminum-backed plates coated with Kieselgel 60 $F_{254}$, from Merck. The chromatograms were visualized using either UV light (UVGL-58, short wavelength), ninhydrin (acidic), or potassium permanganate (basic). Melting points were carried out using a Reichert-Jung Thermo Galen Kopfler block or a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High- and low-resolution fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG AutoSpec Q instrument, with a matrix of *m*-nitrobenzyl alcohol. High- and low-resolution electron impact (EI) mass spectra were recorded using EI ionization at 70 eV, on a VG AutoSpec instrument, equipped with a Fisons autosampler. $^1$H NMR and $^{13}$C NMR spectra were recorded using either JEOL 270 (operating at 270 MHz for $^1$H and 67.8 MHz for $^{13}$C), JEOL Lambda 300 (operating at 300 MHz for $^1$H and 75.4 MHz for $^{13}$C), or JEOL EX 400 (operating at 400 MHz for $^1$H and 100.5 MHz for $^{13}$C) spectrometers. Chemical shifts ($\delta$) are measured in ppm. Spectra were referenced internally using the residual solvent resonance. Coupling constants ($J$) are expressed in hertz, and the multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Only diagnostic peaks have been quoted for proton NMR. Microanalysis was performed with a Perkin-Elmer 240C analyzer. Analytical RP-HPLC was performed with a Beckman System Gold 125 solvent module, equipped with a Beckman System Gold 166 detector ($\lambda = 254$ nm). The column stationary phase was Beckman ultrasphere ODS, 5 $\mu$m (15 cm × 4.6 mm). A mobile phase of [MeOH/0.3% $NH_4CO_3$ (80:20)] was used at a flow rate of 1 mL/min. Infrared spectroscopy was performed

on either a Perkin-Elmer 782 Instrument or a Perkin-Elmer RX 1 FT-IR Instrument. Anhydrous THF, DMF, DCM, and MeOH were purchased from Aldrich. HPLC solvent grade chloroform and MeOH were purchased from Merck. All other solvents used were GPR grade, purchased from Merck or Fisher Scientific. Chemicals were purchased from Aldrich, Fluka, Lancaster, and Acros chemical companies.

Details are given for representative examples **10f** and **15d**. Full experimental details for all compounds are provided as Supporting Information.

**1,3-Bis-*tert*-butoxycarbonyl-1-(4′-chlorobenzyl)-2-methyl-2-thiopseudourea (8b).** To 1,3-bis-*tert*-butoxycarbonyl-2-methyl-2-thiopseudourea (**7**) (2 g, 6.90 mmol) in dry DMF (20 mL) in an ice-bath was added NaH (60% in oil, 0.334 g, 8.36 mmol), and the mixture stirred for 1 h. 4-Chlorobenzyl bromide (1.56 g, 7.60 mmol) was added, and the mixture stirred at room temperature for a further 12 h. Water (30 mL) was added and the mixture extracted with ethyl acetate (3×). The combined organic layers were washed with brine (2×), dried ($Na_2SO_4$), and concentrated to give crude **8b**. Column chromatography [hexane/EtOAc (9:2)] provided pure **8b** (2.21 g, 5.33 mmol, 77%): $R_f$ = 0.42 [hexane/EtOAc (9:2)];$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.36 [s, 9H, C(C*H*$_3$)$_3$], 1.47 [s, 9H, C(C*H*$_3$)$_3$], 2.24 (s, 3H, SC*H*$_3$), 4.68 (s, 2H, C*H*$_2$), and 7.24 (s, 4H, Ar*H*); $^{13}$C NMR (100.5 MHz, $CDCl_3$) $\delta$ 16.0 (S*C*H$_3$), 28.3 [C(*C*H$_3$)$_3$], 28.4 [C(*C*H$_3$)$_3$], 52.0 (*C*H$_2$), 82.0 [*C*(CH$_3$)$_3$], 83.1 [*C*(CH$_3$)$_3$], 128.7 (Ar), 129.4 (Ar), 133.4 (quaternary Ar), 136.0 (quaternary Ar), 151.9 (*C*=O), 157.9 (*C*=O), and 162.7 (*C*=N); FAB$^+$MS *m/z* 415 [(M + 1)$^+$, 30%] and 259 (65); HRMS (FAB) *m/z* 415.1439 (M + 1)$^+$, $C_{19}H_{28}N_2O_4SCl$ requires 415.1458.

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-bis-*tert*-butoxycarbonyl-(*N*-4-chlorobenzyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (9f).** 1,3-Bis-*tert*-butoxycarbonyl-1-(4′-chlorobenzyl-2-methyl-2-thiopseudourea (**8b**) (0.243 g, 0.59 mmol), 5′-amino-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (**6a**) (0.126 g, 0.29 mmol), $HgCl_2$ (0.079 g, 0.29 mmol), triethylamine (0.059 g, 0.082 mL, 0.59 mmol), and DMF (10 mL) were stirred at 50 °C for 24 h. The solution was subsequently filtered and sodium bicarbonate (30 mL) added. The solution was extracted with ethyl acetate and the organic layer washed successively with water and brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give the crude product mixture, which was purified by column chromatography–gradient elution ($CH_2Cl_2$) until unreacted **8b** had been removed then [$CH_3OH/CH_2Cl_2/NH_4OH$ (10:89:1)], affording 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-bis-*tert*-butoxycarbonyl-(*N*-4-chlorobenzyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (0.103 g, 0.13 mmol, 44%): $R_f$ = 0.47 [$CH_3OH/CH_2Cl_2/NH_4OH$ (89:10:1)]; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.16–0.27 [m, 2H, NCH$_2$CH(CH*H*CH*H*)], 0.56–0.68 [m, 2H, NCH$_2$CH(CH*H*CH*H*)], 0.88–1.00 [m, 1H, NCH$_2$C*H*(CH$_2$CH$_2$)], 1.37 [s, 9H, C(C*H*$_3$)$_3$], 1.43 [s, 9H, C(C*H*$_3$)$_3$], 5.60 [s, 1H, C(5)*H*], 6.55 [d, *J* = 8.2 Hz, 1H, C(1)*H*], 6.59 [d, *J* = 8.2 Hz, 1H, C(2)*H*], 6.70 (s, 1H, C(4′)*H*], 6.78 [d, *J* = 8.6 Hz, 1H, C(6′)*H*], 7.21 [d, *J* = 8.6 Hz, 1H, C(7′)*H*], and 7.25–7.48 [m, 4H, Ar*H*]; $^{13}$C NMR (100.5 MHz, $CDCl_3$) $\delta$ 3.4 [NCH$_2$CH-(*C*H$_2$CH$_2$)], 3.9 [NCH$_2$CH(CH$_2$*C*H$_2$)], 9.2 [NCH$_2$*C*H(CH$_2$CH$_2$)], 22.9 [*C*(10)], 27.2 [C(*C*H$_3$)$_3$], 27.6 [*C*(15)], 27.7 [C(*C*H$_3$)$_3$], 28.4 [*C*(8)], 43.5 [*C*(16)], 47.6 (*C*H$_2$Ph), 47.9 [quaternary *C*(13)], 59.1 [*C*(18)], 61.8 [*C*(9)], 72.3 [quaternary *C*(14)], 79.7 [*C*(CH$_3$)$_3$], 82.6 [*C*(CH$_3$)$_3$], 84.3 [*C*(5)], 110.2 (Ar), 111.2 (Ar), 112.0 (Ar), 116.6 (Ar), 118.1 (Ar), 118.4 (Ar), 124.2 (Ar), 126.3 (Ar), 127.8 (Ar), 128.2 (Ar), 129.9 (Ar), 130.1 (Ar), 130.2 (Ar), 130.4 (Ar), 132.8 (Ar), 135.1 (Ar), 135.3 (Ar), 139.0 (Ar), 142.6 (C=O) and 162.7 (*C*=N); FAB$^+$MS *m/z* 796 [(M + 1)$^+$, 100%], 696 (20), and 596 (30); HRMS (FAB) *m/z* 796.3463 (M + 1)$^+$, $C_{44}H_{51}N_5O_7Cl$ requires 796.3477.

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(*N*-4-chlorobenzyl)guanidinyl-3,14-dihydroxyindolo-[2′,3′:6,7]morphinan (10f).** 17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-bis-*tert*-butoxycarbonyl-(*N*-4-chlorobenzyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (**9f**) (0.100 g, 0.13 mmol) was dissolved in dichloromethane (4 mL) and allowed to stir for 10 min at 0 °C. Trifluoroacetic acid (2 mL) was added and the solution allowed to warm to room temperature. Stirring was continued for 12 h, after which the solution was concentrated under reduced pressure. Washing the resultant oil with diethyl ether afforded a precipitate that could be isolated by vacuum filtration. Further purification was achieved by recrystallization (methanol/diethyl ether) to give 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(*N*-4-chlorobenzyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (**10f**) as the bistrifluoroacetic acid salt (0.077 g, 0.09 mmol, 74%): mp 186–189 °C; $R_f$ = 0.13 [$CH_3OH/CH_2Cl_2/NH_4OH$ (89:10:1)]; IR $\nu_{max}$/cm (KBr) 3630–2475 (br, bonded OH and NH) and 1678 (br, C=N, NH and NH$_2$); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.48–0.59 [m, 2H, NCH$_2$CH(CH*H*CH*H*)], 0.73–0.91 [m, 2H, NCH$_2$CH(CH*H*CH*H*)], 1.09–1.22 [m, 1H, NCH$_2$C*H*(CH$_2$CH$_2$)], 5.71 [s, 1H, C(5)*H*], 6.64 [d, *J* = 8.2 Hz, 1H, C(1)*H*], 6.68 [d, *J* = 8.2 Hz, 1H, C(2)*H*], 6.98–7.02 (m, 1H, Ar*H*), and 7.28–7.46 [m, 6H, Ar*H*]; $^{13}$C NMR (100.5 MHz, $CD_3OD$) $\delta$ 3.5 [NCH$_2$CH-(*C*H$_2$CH$_2$)], 6.3 [NCH$_2$CH(CH$_2$*C*H$_2$)], 6.9 [NCH$_2$*C*H(CH$_2$CH$_2$)], 25.1 [*C*(10)], 29.7 [*C*(15)], 30.2 [*C*(8)], 45.3 [*C*(16)], 47.5 [quaternary *C*(13)], 48.0 (*C*H$_2$Ph), 58.9 [*C*(18)], 63.6 [*C*(9)], 73.5 [quaternary *C*(14)], 84.8 [*C*(5)], 109.9 (Ar), 113.7 (Ar), 118.0 (Ar), 119.2 (Ar), 120.5 (Ar), 122.2 (Ar), 122.4 (Ar), 126.6 (Ar), 128.3 (Ar), 129.6 (Ar), 129.7 (Ar), 130.1 (Ar), 132.3 (Ar), 134.4 (Ar), 136.4 (Ar), 138.0 (Ar), 141.8 (Ar), 144.5 (Ar), and 157.5 (*C*=NH); FAB$^+$MS *m/z* 596 [(M + 1)$^+$, 100%]; HRMS (FAB) *m/z* 596.2416 (M + 1)$^+$, $C_{34}H_{35}N_5O_3Cl$ requires 596.2428. Anal. ($C_{34}H_{34}N_5O_3Cl$·2TFA·3H$_2$O) C, H, N.

***N*-Propyl-*N*-cyclopropylmethylthiourea (12d).** Calcium carbonate (1.97 g, 19.67 mmol) was dissolved in $H_2O$ (2 mL) and added to a stirred solution of propylamine (1.16 g, 19.67 mmol) in $CHCl_3$ (30 mL). Thiophosgene (4.52 g, 3 mL, 39.34 mmol) was added and the solution stirred at room temperature for 24 h. The aqueous layer was washed with $H_2O$ and concentrated to give propylisothiocyanate; $R_f$ = 0.72 [EtOAc/hexane (1:1)]. Propylisothiocyanate (0.44 g, 4.38 mmol) was then dissolved in acetone (15 mL) and added dropwise to aminomethylcyclopropane (0.31 g, 4.38 mmol) in acetone (15 mL). The solution was refluxed gently for 3 h, concentrated, and purified by column chromatography [hexane/EtOAc (1:1)], providing the desired *N*-propyl-*N*-cyclopropylmethylthiourea (0.42 g, 2.44 mmol, 56%): $R_f$ = 0.38 [EtOAc/hexane (1:1)]; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.21–0.30 [m, 2H, NCH$_2$-CH(CH*H*CH*H*)], 0.52–0.62 [m, 2H, NCH$_2$CH(CH*H*CH*H*)], 0.97 (t, *J* = 7.3 Hz, 3H, C*H*$_3$), 1.02–1.13 [m, 1H, NCH$_2$C*H*(CH$_2$CH$_2$)], 1.64 [q, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 3.30–3.41 [m, 4H, 2 × NC*H*$_2$], and 6.24 [br s, 2H, 2 × N*H*]; $^{13}$C NMR (67.8 MHz, $CDCl_3$) $\delta$ 3.5 [NCH$_2$CH(*C*H$_2$CH$_2$)] and [NCH$_2$CH(CH$_2$*C*H$_2$)], 10.0 [NCH$_2$*C*H(CH$_2$CH$_2$)], 11.3 (*C*H$_3$), 22.1 (*C*H$_2$CH$_3$), 45.9 (N*C*H$_2$), 49.4 (N*C*H$_2$CH), and 181.0 (*C*=S); FAB$^+$MS *m/z* 173 [(M + 1)$^+$, 100%]; HRMS (FAB) *m/z* 173.1116 (M + 1)$^+$, $C_8H_{17}N_2S$ requires 173.1112.

***N*-*tert*-Butoxycarbonyl-*N*-propyl-*N*-cyclopropylmethylthiourea (13d).** *N*-Propyl-*N*-cyclopropylmethylthiourea (**12d**) (0.41 g, 2.38 mmol) was added to NaH (0.19 g, 60% in oil, 4.75 mmol) in THF (40 mL) at 0 °C and stirred for 10 min. (*tert*-Butoxycarbonyl)$_2$O (0.60 g, 2.73 mmol) was added and the mixture stirred at room temperature for 12 h before addition of 10% NaOH and stirring for 20 min. The organic layer was then separated and the aqueous layer further extracted with EtOAc. The combined organic layers were concentrated and subsequently treated with hexane, which caused unreacted starting material to precipitate out. The solid was removed by filtration and the filtrate subsequently purified by column chromotography [EtOAc/hexane (1:3)], yielding the *N*-*tert*-butoxycarbonyl-*N*-propyl,*N*-cyclopropylmethylthiourea (0.30 g, 1.09 mmol, 46%): $R_f$ = 0.66 [EtOAc/hexane (1:3)]; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.22–0.49 [m, 4H, NCH$_2$CH(CH*H*CH*H*) and NCH$_2$CH(CH*H*CH*H*)], 0.51–0.57 [m, 1H, NCH$_2$C*H*(CH$_2$-CH$_2$)], 0.88 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.51 [s, 9H, C(C*H*$_3$)$_3$], 1.65 [q, *J* = 7.4 Hz, 2H, C*H*$_2$CH$_3$], 3.39–3.60 (m, 2H, NHC*H*$_2$), 4.16–4.30 (m, 2H, CONC*H*$_2$), and 10.86 (br s, 1H, N*H*); $^{13}$C NMR (100.5 MHz, $CDCl_3$) $\delta$ 4.0 [NCH$_2$CH(*C*H$_2$CH$_2$)], 4.1 [NCH$_2$CH(CH$_2$*C*H$_2$)], 11.0 [NCH$_2$*C*H(CH$_2$CH$_2$)], 11.7 (*C*H$_3$),

22.3 ($CH_2CH_3$), 28.4 [$C(CH_3)_3$], 51.1 ($HNCH_2$), 57.2 ($CONCH_2$), 83.3 [$C(CH_3)_3$], 151.7 (C=O), and 183.0 (C=S); FAB+MS *m/z* 273 [$(M + 1)^+$, 25%] and 217 (85); HRMS (FAB) *m/z* 273.1644 $(M + 1)^+$, $C_{13}H_{25}N_2O_2S$ requires 273.1637.

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-*tert*-butoxycarbonyl-(*N*-propyl-*N*′-cyclopropylmethyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (14d).** *N*-*tert*-Butoxycarbonyl-*N*-propyl-*N*-cyclopropylmethylthiourea (**13d**) (0.152 g, 0.56 mmol), 5′-amino-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (**6a**) (0.120 g, 0.28 mmol), $HgCl_2$ (0.152 g, 0.56 mmol), triethylamine (0.028 g, 0.040 mL, 0.28 mmol), and DMF (10 mL) were added together at 5°C under $N_2$ before being stirred at 50 °C for 48 h. The solution was subsequently filtered and sodium bicarbonate (30 mL) added. The solution was extracted with ethyl acetate and then washed successively with water and brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give the crude product mixture, which was purified by column chromatography–gradient elution ($CH_2Cl_2$) until unreacted **13d** had been removed and then [$CH_3OH/CH_2Cl_2/NH_4OH$ (10:89:1)], affording 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-*tert*-butoxycarbonyl-(*N*-propyl-*N*′-cyclopropylmethyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]-morphinan (0.062 g, 0.09 mmol, 33%): $R_f$ = 0.61 [$CH_3OH/CH_2Cl_2/NH_4OH$ (89:10:1)]; $^1H$ NMR (270 MHz, $CDCl_3$) δ 0.05–0.10 [m, 2H, $NCH_2CH(CHHCHH)$], 0.11–0.20 [m, 2H, $NCH_2CH(CHHCHH)$], 0.35–0.44 [m, 2H, $NCH_2CH(CHHCHH)$],0.46–0.58 [m, 2H, $NCH_2CH(CHHCHH)$], 0.73–0.83 [m, 1H, $NCH_2CH(CH_2CH_2)$], 0.84–0.98 [m, 1H, $NCH_2CH(CH_2CH_2)$], 1.47 [s, 9H, $C(CH_3)_3$], 5.60 [s, 1H, C(5)*H*], and 6.38–7.10 (m, 5H, Ar*H*); $^{13}C$ NMR (67.8 MHz, $CDCl_3$) δ 3.3 [$NCH_2CH(CH_2CH_2)$], 3.4 [$NCH_2CH(CH_2CH_2)$], 3.8 [$NCH_2CH(CH_2CH_2)$], 3.9 [$NCH_2CH(CH_2CH_2)$], 9.4 [$NCH_2CH(CH_2CH_2)$], 10.5 [$NCH_2CH(CH_2CH_2)$], 11.4 ($CH_3$), 21.8 ($CH_2$), 23.1 [C(10)], 28.3 [$C(CH_3)_3$], 28.8 ($CH_2$), 31.4 ($CH_2$), 43.6 ($CH_2$), 47.9 [quaternary C(13)], 59.5 [C(18)], 62.4 [C(9)], 72.7 [quaternary C(14)], 81.0 [quaternary $C(CH_3)_3$], 85.0 [C(5)], 110.7 (Ar), 111.7 (Ar), 117.5 (Ar), 117.9 (Ar), 118.5 (Ar), 124.5 (Ar), 127.3 (Ar), 129.6 (Ar), 130.6 (Ar), 134.2 (Ar), 139.6 (Ar), 143.4 (Ar), 153.9 (Ar), and 154.1 (C=N); FAB+MS *m/z* 668 [$(M + 1)^+$, 100%] and 568 (30); HRMS (FAB) *m/z* 668.3819 $(M + 1)^+$, $C_{39}H_{50}N_5O_5$ requires 668.3812.

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(*N*-propyl-*N*′-cyclopropylmethylthiourea)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (15d).** 17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-*tert*-butoxycarbonyl-(*N*-propyl-*N*′-cyclopropylmethyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (**14d**) (0.046 g, 0.07 mmol) was treated as described for **10f**, to give 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(*N*-propyl-*N*′-cyclopropylmethyl)-guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]morphinan (**15d**) as the bistrifluoroacetic acid salt (0.039 g, 0.07 mmol, 99%): mp 177–178 °C; $R_f$ = 0.24 [$CH_3OH/CH_2Cl_2/NH_4OH$ (89:10:1)]; IR $\nu_{max}$/cm (KBr) 3700–2620 (br, bonded OH and NH) and 1678 (br, C=N, NH and $NH_2$); $^1H$ NMR (400 MHz, $CD_3OD$) δ 0.12–0.21 [m, 2H, $NCH_2CH(CHHCHH)$], 5.65 [s, 1H, C(5)*H*], 6.56 [d, *J* = 8.2 Hz, 1H, C(1)*H*], 6.59 [d, *J* = 8.2 Hz, 1H, C(2)*H*], 6.93 [dd, $J_1$ = 8.6 Hz, $J_2$ = 1.9 Hz, 1H, C(6′)*H*], 7.25 [d, *J* = 1.9 Hz, 1H, C(4′)*H*], and 7.38 [d, *J* = 8.6 Hz, 1H, C(7′)*H*]; $^{13}C$ NMR (100.5 MHz, $CD_3OD$) δ 3.7 [$NCH_2CH(CH_2CH_2)$], 4.2 [$NCH_2CH(CH_2CH_2)$], 6.5 [$NCH_2CH(CH_2CH_2)$], 7.1 [$NCH_2CH(CH_2CH_2)$], 11.5 [$NCH_2CH(CH_2CH_2)$], 11.7 ($CH_3$), 23.6 [C(10)], 25.3 ($CH_2$), 30.0 ($CH_2$), 30.5 ($CH_2$), 44.6 [C(16)], 47.6 ($CH_2$), 47.9 [quaternary C(13)], 59.2 [C(18)], 63.9 [C(9)], 73.9 [quaternary C(14)], 85.2 [C(5)], 110.3 (Ar), 114.2 (Ar), 118.6 (Ar), 119.7 (Ar), 120.9 (Ar), 122.8 (Ar), 122.9 (Ar), 127.4 (Ar), 129.0 (Ar), 130.6 (Ar), 132.9 (Ar), 138.5 (Ar), 142.4 (Ar), 145.1 (Ar), and 156.6 (C=N); FAB+MS *m/z* 568 [$(M + 1)^+$, 100%]; HRMS (FAB) *m/z* 568.3275 $(M + 1)^+$, $C_{34}H_{42}N_5O_3$ requires 568.3288. Anal. ($C_{34}H_{41}N_5O_3 \cdot 2TFA \cdot 2H_2O$) C, H, N.

**Biological Methods.** The methods utilized have been reported previously.[29]

**Acknowledgment.** This work was supported by NIDA Grants DA 07315 and DA00254, and ligand binding and [$^{35}S$]GTPγS assays were provided by NIDA–OTDP.

**Supporting Information Available:** Spectra and experimental procedures for all compounds. This material is available free of charge via the Internet at https://pubs.acs.org.

## References

(1) Schenk, S.; Partridge, B.; Shippenberg, T. S. U69593, a kappa opioid agonist, decreases cocaine self-administration and decreases cocaine-produced drug-seeking. *Psychopharmacology* **1999**, *144*, 339–346.
(2) Mello, N. K.; Negus, S. S. Effects of kappa opioid agonists on cocaine- and food-maintained responding by rhesus monkeys. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 812–824.
(3) Archer, S.; Glick, S. D.; Bidlack, J. Cyclazocine revisited. *Neurochem. Res.* **1996**, *21*, 1369–1373.
(4) Heidbreder, C. A.; Babovic-Vuksanovic, D.; Shoaib, M.; Shippenberg, T. S. Development of behavioural sensitisation to cocaine: Influence of kappa opioid receptor agonists. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 150–163.
(5) Shippenberg, T. S.; LeFavour, A.; Heidbreder, C. A. Kappa opioid receptor agonists prevent sensitisation to the conditioned rewarding effects of cocaine. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 545–554.
(6) Spealman, R. D.; Bergman, J. Opioid modulation of the discriminative stimulus effects of cocaine: Comparison of mu, kappa and delta agonists in squirrel monkeys discriminating low doses of cocaine. *Behav. Pharmacol.* **1994**, *5*, 21–31.
(7) Vink, R.; Portoghese, P. S.; Faden, A. I. Kappa opioid antagonist improves cellular bioenergetics and recovery after traumatic brain injury. *Am. J. Physiol.* **1991**, *261*, R1527–R1532.
(8) Newman, D. D.; Rajakumar, N.; Flumerfelt, B. A.; Stoessl, A. J. A kappa opioid antagonist blocks sensitisation in a rodent model of Parkinson's disease. *Neuroreport* **1997**, *8*, 669–672.
(9) Mague, S. D.; Pliakas, A. M.; Todtenkopf, M. S.; Tomasiewicz, H. C.; Zhang, Y.; Stevens Jr, W. C.; Jones, R. M.; Portoghese, P. S.; Carlezon Jr., W. A. Antidepressant-like effects of κ-opioid receptor antagonists in the forced swim test in rats. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 323–330.
(10) Arjune, D.; Bodnar, R. J. Suppression of nocturnal, palatable and glucoprivic intake in rats by the kappa opioid antagonist, nor-binaltorphimine. *Brain Res.* **1990**, *534*, 313–316.
(11) Katafuchi, T.; Hattori, Y.; Nagatomo, I.; Koizumi, K. Kappa opioid antagonist strongly attenuates drinking of genetically polydipsic mice. *Brain Res.* **1991**, *546*, 1–7.
(12) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Bimorphinans as highly selective, potent κ-opioid receptor antagonists. *J. Med. Chem.* **1987**, *30*, 238–239.
(13) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Binaltorphimine and nor-binaltorphimine, potent and selective kappa-opioid receptor antagonists. *Life Sci.* **1987**, *40*, 1287–1292.
(14) Takemori, A. E.; Ho, B. Y.; Naeseth, J. S.; Portoghese, P. S. Norbinaltorphimine, a highly selective kappa-opioid antagonist in analgesic and receptor-binding assays. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 255–258.
(15) Jones, R. M.; Hjorth, S. A.; Schwartz, T. W.; Portoghese, P. S. Mutational evidence for a common kappa antagonist binding pocket in the wild-type kappa and mutant mu[K303E] opioid receptors. *J. Med. Chem.* **1998**, *41*, 4911–4914.
(16) Jones, R. M.; Portoghese, P. S. 5′-Guanidinonaltrindole, a highly selective and potent κ-opioid receptor antagonist. *Eur. J. Pharmacol.* **2000**, *396*, 49–52.
(17) Negus, S. S.; Mello, N. K.; Linsenmayer, D. C.; Jones, R. M.; Portoghese, P. S. Kappa opioid antagonist effects of the novel kappa antagonist 5′-guanidinonaltrindole (GNTI) in an assay of schedule-controlled behavior in rhesus monkeys *Psychopharmacology* **2002**, *163*, 412–419.
(18) Grundt, P.; Jales, A. J.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M. 14-Amino, 14-alkylamino- and 14-acylamino analogues of oxymorphindole. Differential effects on opioid receptor binding and functional profiles. *J. Med. Chem.* **2003**, *46*, 1563–1566.
(19) Korlipara, V. L.; Takemori, A. E.; Portoghese, P. S. Electrophilic N-benzylnaltrindoles as δ-opioid receptor-selective antagonists. *J. Med. Chem.* **1995**, *38*, 1337–1343.
(20) Korlipara, V. L.; Takemori, A. E.; Portoghese, P. S. N-Benzylnaltrindoles as long-acting δ-opioid receptor antagonists. *J. Med. Chem.* **1994**, *37*, 1882–1885.
(21) Comer, S. D.; Burke, T. F.; Lewis, J. W.; Woods, J. H. Cloccinamox: A novel, systemically active, irreversible opioid antagonist. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 1051–1056.

(22) Burke, T. F.; Woods, J. H.; Lewis, J. W.; Medzihradsky, F. Irreversible opioid antagonist effects of clocinnamox on opioid analgesia and mu receptor binding in mice. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 715−721.
(23) Zernig, G.; Butelman, E.; Lewis, J. W.; Walker, E. A.; Woods, J. H. In vivo determination of mu opioid receptor turnover in rhesus monkeys after irreversible blockade with clocinnamox. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 57−65.
(24) Stevens, W. C.; Jones, R. M.; Subramanian, G.; Metzger, T. G.; Ferguson, D. M.; Portoghese, P. S. Potent and selective indolomorphinan antagonists of the kappa-opioid receptor. *J. Med. Chem.* **2000**, *43*, 2759−2769.
(25) Bender, D. M.; Williams, R. M. An efficient synthesis of (S)-m-tyrosine. *J. Org. Chem.* **1997**, *62*, 6690−6691.
(26) Kashdan, D. S.; Schwartz, J. A.; Rapoport, H. Synthesis of 1,2,3,4-tetrahydroisoquinolines. *J. Org. Chem.* **1982**, *47*, 2638−2643.
(27) Levallet, C.; Lerpiniere, J.; Ko, S. Y. The $HgCl_2$ promoted guanylation reaction: The scope and limitations. *Tetrahedron* **1997**, *53*, 5291−5304.
(28) Traynor, J. R.; Nahorski, S. R. Modulation by mu-opioid agonists of guanosine-5′-O-(3-[S-35]thio)triphosphate binding to membranes from human neuroblastoma SH−SY5Y cells. *Mol. Pharmacol.* **1995**, *47*, 848−854.
(29) Toll, L.; Berzetei-Gurske, I. P.; Polgar, W. E.; Brandt, S. R.; Adapa, I. D.; Rodriguez, L.; Schwartz, R. W.; Haggart, D.; O'Brien, A.; White, A.; Kennedy, J. M.; Craymer, K.; Farrington, L.; Auh, J. S. Standard binding and functional assays related to (NIDA) Medications Development Division testing for potential cocaine and narcotic treatment programs. *NIDA Res. Monogr. Ser.* **1998**, *178*, 440−466.
(30) Butelman, E. R.; Harris, T. J.; Kreek, M. J. Effects of E-2078, a stable dynorphin A(1−8) analogue on sedation and serum prolactin levels in rhesus monkeys. *Psychopharmacology* **1999**, *147*, 73−80.

JM0309203

# Major Effect of Pyrrolic N-Benzylation in Norbinaltorphimine, the Selective κ-Opioid Receptor Antagonist

Cédric Chauvignac,† Carl N. Miller,‡ Sanjay K. Srivastava,† John W. Lewis,† Stephen M. Husbands,*,† and John R. Traynor‡

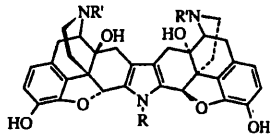
*Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK, and Department of Pharmacology, University of Michigan, Ann Arbor, Michigan 48109*

*Received October 15, 2004*

Indolic N-benzylation of naltrindole reportedly extends the duration of δ-opioid receptor (DOR) antagonism. Similar modification of the κ-opioid receptor (KOR) antagonist norBNI (**1a**) and its 17,17′-diNMe analogue (**1d**), a low potency μ-opioid receptor (MOR) partial agonist, was found to affect predominantly their MOR activity. When administered systemically in mouse antinociceptive assays, *N*-benzyl-norBNI (**1b**) had only MOR agonist activity of relatively short duration whereas on central administration it had only a KOR-antagonist action of extremely long duration.

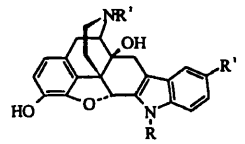
## Introduction

For the past 30 years there has been considerable interest in the development of nonpeptidic ligands for κ (KOR) and δ (DOR) opioid receptors. Discovery of antagonists with selectivity for KOR[1–3] and DOR[1,4] has enabled the function of these receptor systems to be explored. The prototype KOR antagonist norBNI (**1a**) was designed on the message–address principle in which the address component which confers KOR selectivity is the basic nitrogen of the second *N*-cyclopropylmethyl (CPM) group.[5] The follow-up to norBNI was GNTI (**2b**) in which the guanidino KOR address component was introduced into the selective DOR-antagonist, naltrindole (NTI, **2a**).[6] The effect of benzyl substitution at the indole N-atom in NTI to give BNTI (**2c**) was to bring selectivity for the putative $DOR_2$-subtype in an antagonist of substantially longer duration than NTI.[7] It was thus of interest to investigate the effect of equivalent N-benzylation of norBNI (**1a**) and its 17,17′-diNMe analogue (**1d**). Herein we report the results of the in vitro (binding and [$^{35}$S]GTPγS) pharmacological evaluation of **1b** and analogues, plus the further evaluation of **1b** in vivo.



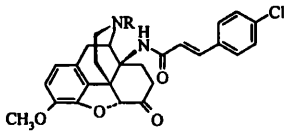
**1**

a: R = H, R′ = $CH_2cC_3H_5$
b: R = $CH_2C_6H_5$, R′ = $CH_2cC_3H_5$
c: R = $CH_3$, R′ = $CH_2cC_3H_5$
d: R = H, R′ = $CH_3$
e: R = $CH_2C_6H_5$, R′ = $CH_3$



**2**

a: R = R¹ = H, R² = $CH_2cC_3H_5$, NTI
b: R = H, R¹ = NHC(=NH)$NH_2$, R² = $CH_2cC_3H_5$, GNTI
c: R = $CH_2C_6H_5$, R¹ = H, R² = $CH_2cC_3H_5$, BNTI
d: R = R¹ = H, R² = $CH_3$, OMI
e: R = H, R¹ = NHC(=NH)$NH_2$, R² = $CH_3$



**3**

a: R = $CH_2cC_3H_5$
b: R = $CH_3$

**Chemistry.** Two complimentary methods were utilized for the synthesis of BnorBNI (**1b**). In the first, the reported method for the synthesis of BNI (**1c**) from naltrexone (**4**) and *N*-methylhydrazine sulfate[8] was modified by the use of *N*-benzylhydrazine sulfate and extending the reaction time to one week, then at elevated temperature for 2 days. Unfortunately, under these conditions only 1% of **1b** could be isolated with the major identifiable material appearing to be hydrazone (**5**) in 20% yield (Scheme 1). The alternative method, direct benzylation of **1a** (prepared from naltrexone in 62% yield)[9] using excess sodium hydride and benzyl bromide, yielded a mixture of tri- and pentabenzyl-substituted norBNI, that was hydrolyzed immediately in hydrochloric acid/methanol to yield **1b** in 63% yield (39% from naltrexone). Similar treatment of **1d**, prepared from oxymorphone (**4b**), with benzyl bromide yielded the tribenzyl-substituted compound that was hydrolyzed to **1e** with HBr/MeOH.

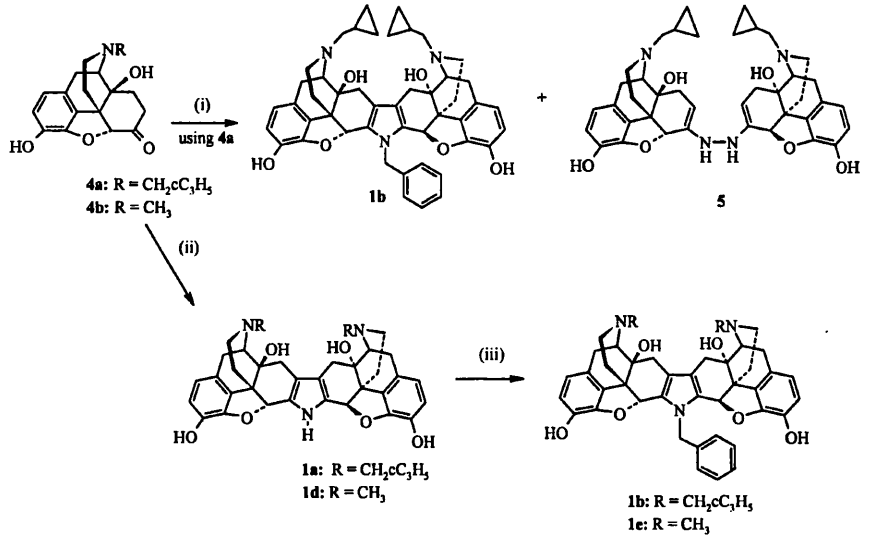
## Results and Discussion

Affinities of the compounds for opioid receptors were measured using radioligand binding assays in membranes from C6μ, C6δ, and CHOκ cells and competition for the nonselective antagonist [$^3$H]diprenorphine as previously described.[10] BnorBNI (**1b**) had subnanomolar affinity for KOR with modest selectivity over MOR and DOR (Table 1). When compared with norBNI (**1a**), the prototypic KOR-antagonist **1b** was as, or slightly more, selective under these conditions. The modest selectivity observed for these compounds was not surprising since Takemori et al.[3] showed that binaltorphimine (BNI, **1c**) had very little KOR selectivity in binding assays. The 17-NMe analogues (**1d**, **1e**) had at least an order of

* Corresponding author. Tel: (1225) 383103. Fax: (1225) 386114. E-mail: s.m.husbands@bath.ac.uk.
† University of Bath.
‡ University of Michigan.

10.1021/jm049172n CCC: $30.25 
Published on Web 02/09/2005

**Scheme 1**[a]




[a] Reagents and conditions: (i) $BnHNNH_2.H_2SO_4$, AcOH (ii) $H_2NNH_2$, DMF, 100 °C then $MeSO_3H$, DMSO, 130 °C (iii) NaH, 18-crown-6, BnBr then methanol, 12 N HCl, 90 °C (for **1b**), HBr, r.t. (for **1e**).

**Table 1.** Binding Affinities for Ligand Binding to Opioid Receptors[a]

| | $K_i$ (nM) ± SEM[b] | | | | |
|---|---|---|---|---|---|
| compound | MOR | DOR | KOR | MOR/KOR | DOR/KOR |
| **1a**, norBNI | 1.20 ± 0.2 | 5.8 ± 0.645 | 0.4 ± 0.06 | 3 | 15 |
| **1b**, BnorBNI | 10.0 ±2.5 | 8.6 ± 0.7 | 0.7 ± 0.1 | 14 | 12 |
| **1d** | 63.6 ± 39.1 | 98.2 ± 25.3 | 7.7 ± 1.0 | 8 | 13 |
| **1e** | 6.4 ± 1.1 | 207 ± 96 | 24.9 ± 5.6 | 0.3 | 8 |

[a] Rat MOR or DOR receptors in C6 cells and human KOR receptors in CHO cells. [b] Values are the mean of three experiments, each performed in duplicate. Experiments were performed as described in ref 10 using [$^3$H]diprenorphine.

**Table 2.** Agonist Effects of Ligands at Opioid Receptors Measured by the [$^{35}$S]GTPγS Binding Assay[g]

| | $EC_{50}$/nM, % stim | | | | |
|---|---|---|---|---|---|
| compd | MOR[a] | | DOR[b] | KOR[c] | |
| **1a** | -[e] | | -[e] | -[e] | |
| **1b** | 187[d] | 38 | -[e] | 1906[f] | 29 |
| **1d** | 1388 ± 370 | 66 | -[e] | -[e] | |
| **1e** | 526 ± 279 | 54 | -[e] | -[e] | |

[a] Compared to the full agonist DAMGO. [b] Compared to the full agonist SNC80. [c] Compared to the full agonist U69593. [d] 95% CI 42-844nM. [e] No stimulation up to 10 000 nM. [f] 95% CI 269-13490 nM. [g] Experiments were performed using membranes from Rat MOR or DOR receptors in C6 cells and human KOR receptors in CHO cells as described in ref 11. Values are from three separate experiments.

magnitude lower affinity than **1a** and **1b** at each receptor. The exception was for **1e** at the MOR where affinity was similar to **1b**, resulting in **1e** displaying modest selectivity for MOR.

In the [$^{35}$S]GTPγS functional assay[10,11] in C6μ, C6δ, and CHOκ cells Bnor BNI (**1b**) showed partial MOR and KOR agonism, reaching approximately 40% and 30% respectively of maximal effect compared with the appropriate full agonists at each receptor (Table 2). The MOR partial agonist effect of BnorBNI, though of modest potency, was ten-times higher than its potency as a KOR-partial agonist. In contrast, there are no unequivocal reports in the literature that **1a** or **1c** have opioid agonist actions in vitro or in vivo, with evidence only of very limited agonism in isolated tissue assays.[12] However, Takemori et al.[3] reported that 24.5 μmol/kg **1a** sc enhanced the potency of the selective peptidic MOR agonist DAMGO 3-fold in the acetic acid induced stretching assay in mice (AS).[3] As expected from standard opioid SAR regarding 17-NMe and 17-NCPM substituents, **1d** and **1e** had higher efficacy at MOR than norBNI (**1a**) and BnorBNI (**1b**) but were substantially less potent. However, the additional benzyl group in **1e** increased MOR potency rather than efficacy compared to **1d**, which is in contrast to the **1a**/**1b** comparison where the additional benzyl group increased MOR efficacy. The activity of **1d** in the [$^{35}$S]GTPγS assay, low potency MOR partial agonist, is in agreement with that of Portoghese's group who found similar activity in the guinea pig ileum assay.[9]

The antagonist potency of BnorBNI (**1b**) determined against the selective KOR agonist U69593 ($K_e$ = 0.26 nM) was 50-fold greater than its potency determined against the selective DOR agonist SNC80 and nearly 100-fold greater than its potency against the MOR agonist DAMGO (Table 3). Once again these data for BnorBNI (**1b**) compare favorably with those obtained for norBNI (**1a**) (50- and 22- fold selective for KOR over DOR and MOR respectively) under the same assay conditions. Thus, the selectivity of the KOR antagonist action of both norBNI and BnorBNI is substantially greater in this functional assay than their KOR-selectivity in binding assays. The 17-NMe analogues (**1d**, **1e**) were very much less potent KOR antagonists than norBNI and BnorBNI to the extent of 2−3 orders of magnitude (Table 3).

It is of interest to compare the binding and in vitro effects of 17-N-Me versus 17-N-CPM substitution in the

**Table 3.** Antagonist Effects of Ligands at Opioid Receptors Measured by the [$^{35}$S]GTPγS Binding Assay[b]

| compd | $K_e$ (± SEM)/nM | | |
|---|---|---|---|
| | MOR[a] | DOR[a] | KOR[a] |
| **1a** | 2.38 ± 0.58 | 5.17 ± 0.73 | 0.11 ± 0.01 |
| **1b** | 25.5 ± 2.3 | 13.3 ± 4.5 | 0.26 ± 0.085 |
| **1d** | NT | NT | 27.0 ± 4.3 |
| **1e** | NT | NT | 311 ± 30 |

[a] $K_e$ values were determined from dose–response curves for DAMGO (MOR), SNC80 (DOR), and U69593 (KOR) in the presence or absence of test ligand according to the formula: $K_e$ = [antagonist]/(dose-ratio − 1). [b] Experiments were performed using membranes from Rat MOR or DOR receptors in C6 cells and human KOR receptors in CHO cells as described in ref 11. Values are from 3 separate experiments.

current series with equivalent substitutions in series of selective OR ligands having indolomorphinan structures. The 17-NMe analogue (**2e**) of GNTI (**2b**) in binding assays had substantially lower KOR affinity than GNTI but greater KOR selectivity as a result of even lower MOR and DOR affinity.[13] This was also true of OMI (**2d**) in comparison to NTI.[14,15] In the present series the loss of affinity in substituting 17-NCPM by NMe is similar for KOR and DOR so that there is no gain of KOR over DOR selectivity. There was a small gain of KOR over MOR selectivity from norBNI (**1a**) to **1d**, but the reverse was true when the pyrrolic *N*-benzyl group was introduced (**1e** versus **1b**).

The effects on the in vitro OR functional profiles of GNTI (**2b**) and NTI (**2a**) when the 17-NCPM group is exchanged for NMe are quite different. The analogue (**2e**) of GNTI remains a KOR antagonist but with very much lower potency and selectivity than GNTI; there was no evidence of agonist activity in isolated tissue preparations.[13] By contrast, the selective, potent DOR antagonist activity of NTI (**2a**) was totally lost in OMI (**2d**) but the latter had substantial DOR partial agonist activity.[15] In the present series the effects of 17-NMe for 17-NCPM substitution in norBNI (**1d** cf. **1a**) was reduction of KOR antagonist potency as in NTI but of greater significance was the appearance of a MOR partial agonist effect of substantial efficacy though of low potency. The latter was increased by introduction of the pyrrolic *N*-benzyl group (in **1e**).

The action of BnorBNI (**1b**) at opioid receptors was further investigated in vivo in the mouse tail withdrawal assay for antinociception (TW), in which the water temperature was 50 °C (Table 4).[16] When **1b** (10 mg/kg) was administered subcutaneously (sc) 1 h or 3 h before U69593 (sc), the dose–response curve of the agonist was shifted 2.6-fold to lower doses, suggesting an additive antinociceptive effect of **1b**. By 24 h the effect was no longer significant and at no time point (up to 48 h) was an antagonist effect detected, or at 24 h with 32 mg/kg **1b**. In contrast, norBNI (**1a**: 32 mg/kg sc, 24 h pretreatment) gave a 4-fold rightward shift of the dose–response curve for U69593.

Administration (sc) of BnorBNI (**1b**) alone in TW gave a substantial antinociceptive effect measured 30 min or 1 h after administration, but there was no significant effect by 3 h. The antinociceptive effect of BnorBNI (**1b**) was not inhibited by norBNI (**1a**) (data not shown) but was antagonized by the selective MOR antagonist methocinnamox (M-CAM)[16] (Figure 1), indicating it was mediated by an agonist effect at MOR. In contrast

**Table 4.** Effect of Ligands on the Dose–Effect Curve for U69593 Administered sc in the Warm Water Tail Withdrawal Assay (TW) after Systemic (sc) or Central (icv) Administration[a]

| route of admin | treatment conditions applied to U69593 | $EC_{50}$, mg/kg | fold shift | shift significance $p$ value[c] |
|---|---|---|---|---|
| | +vehicle at −1 h[b] | 5.2 | — | — |
| sc | +10 mg/kg **1b** at −1 h | 2.0 | −2.56 | 0.0002 |
| sc | +10 mg/kg **1b** at −3 h | 2.1 | −2.55 | 0.0145 |
| sc | +10 mg/kg **1b** at −18 h | 9.0 | 1.73 | n.s. |
| sc | +10 mg/kg **1b** at −24 h | 4.4 | −1.17 | n.s. |
| sc | +32 mg/kg **1b** at −24 h | 5.7 | 1.09 | n.s. |
| sc | +10 mg/kg **1b** at −48 h | 9.9 | 1.90 | n.s. |
| sc | +32 mg/kg **1a** at −24 h | 22.7 | 4.12 | 0.0003 |
| icv | +10 nmol **1b** at −1 h | 49.1 | 9.41 | <0.0001 |
| icv | +10 nmol **1b** at −24 h | 26.3 | 5.04 | 0.0003 |
| icv | +10 nmol **1b** at −48 h | 74.2 | 14.22 | <0.0001 |
| icv | +10 nmol **1b** at −168 h | 37.0 | 7.09 | <0.0001 |
| icv | +10 nmol **1a** at −24 h | 31.8 | 6.10 | <0.0001 |

[a] Assays were performed as previously described in ref 12. Negative shift values reflect a leftward shift; positive values reflect a rightward shift. Significance of the shifts in agonist effect was determined by 2-way ANOVA. [b] Vehicle is 10% DMSO in normal saline. [c] n.s. = not significant.

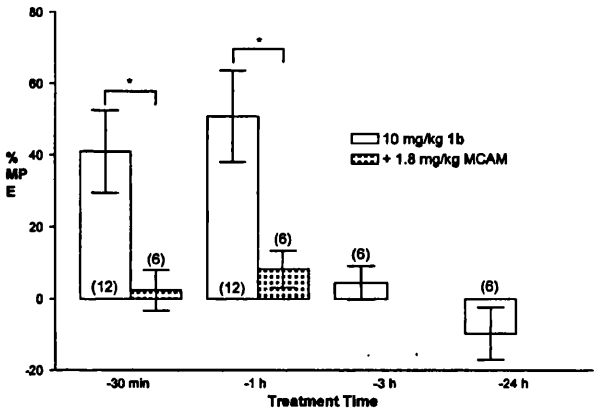



**Figure 1.** Agonist activity of BnorBNI (**1b**) in the tail withdrawal assay.

norBNI (**1a**) has no antinociceptive activity in the AS antinociceptive assay when administered sc but is an effective and selective KOR antagonist.[17]

When administered icv, BnorBNI (**1b**) had no agonist effect in the TW test but was an effective and selective KOR antagonist lasting at least 168 h, with the peak effect around 48 h (Table 4). The antagonist selectivity of BnorBNI (**1b**) (icv) was assessed after 1 h pretreatment by comparison of its ability to antagonize U69593 (KOR) compared with its antagonism of SNC80 (DOR) and morphine (MOR). In the case of SNC80 the water temperature in TW was set at 48 °C since DOR agonists have very little antinociceptive effect at higher temperatures. Compared with the 9-fold shift in the U69593 dose–effect curve there was no inhibition of the agonist effects of SNC80 and morphine in the presence of 10 nmoles BnorBNI (**1b**) (data not shown). This confirms that BnorBNI (**1b**) is a substantially selective KOR antagonist under these conditions, in accord with its selectivity as a KOR antagonist in the [$^{35}$S]GTPγS assay. At 24 h pretreatment the shift in the U69593 dose–response curve produced by 10 nmol of BnorBNI (**1b**) icv was similar to that of 10 nmol of norBNI (**1a**) (Table 4). The lack of agonist action on direct central administration of BnorBNI (**1b**) is surprising, but there

are other examples of opioid ligands with agonist and antagonist effects that exhibit agonism only when administered systemically. The 14-cinnamoylaminocodeinone (**3b**) when administered sc showed very potent and efficacious MOR-mediated antinociceptive effects in TW with no evidence of delayed antagonism.[18] In contrast on icv administration this same compound was without antinociceptive effects, but was a potent, delayed morphine antagonist.[19]

In conclusion, the effect of introducing a benzyl substituent to the pyrrole-N of norBNI (**1a**) and its 17-NMe analogue (**1d**) was predominantly on their MOR pharmacology. In the former case, the effect was to increase MOR efficacy, but not potency, while in the latter, MOR potency was increased but with no effect on efficacy. Unlike norBNI (**1a**), BnorBNI (**1b**) acts as a partial MOR agonist in vitro that shows an antinociceptive effect of relatively short duration when administered systemically. However, when administered centrally the compound lacks this effect and instead is a selective KOR antagonist of very long duration, comparable to norBNI (**1a**).

## Experimental Section

**Chemistry.** Reagents and solvents were purchased from Aldrich or Lancaster. Melting points were recorded on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High and low resolution fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG AutoSpec Q instrument, with a matrix of *m*-nitrobenzyl alcohol. Microanalyses were performed with a Perkin-Elmer 240C analyzer.

**17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-4,5:4′,5′-diepoxy-6,6′-(benzylimino)[7,7′-bimorphinan]-3,3′,14,14′-tetrol (1b).** To a solution of norBNI[2] (0.30 g: 0.45 mmol) in dry THF under a $N_2$ atmosphere were added NaH (0.18 g: 4.52 mmol) and 18-crown-6 (30 mg: 0.11 mmol). This mixture was stirred for 20 min at r.t. before adding BnBr (0.16 mL: 1.36 mmol) and stirring continued for a further 43 h. The reaction was quenched by the addition of $H_2O$, the organic layer collected and dried ($MgSO_4$), and solvent removed in vacuo. The crude oil was purified by column chromatography ($CH_2Cl_2$:MeOH:$NH_4OH$ 400:10:1 to 290:10:1) to yield a mixture of tri- and pentabenzyl-substituted norBNI (0.33 g). This mixture was dissolved in MeOH/cHCl (20 mL, 1:1) and heated to 90 °C for 40 h. Cooling, basification (aqueous ammonia), and removal of the precipitate by filtration was followed by evaporation of the filtrate to dryness. Column chromatography ($CH_2Cl_2$:MeOH:$NH_4OH$ 200:10:1) yielded BnorBNI as an off-white solid (0.21 g: 63%), MS (FAB): $m/z$ = 752 $(M + H)^+$, HRMS (FAB) $m/z$ 752.3715 $(M + H)^+$, $C_{47}H_{49}N_3O_6$ requires 751.3620, $R_f$ ($CH_2Cl_2$/MeOH/$NH_4OH$:110/10/1) = 0.76, mp > 240°C, Anal. ($C_{47}H_{49}N_3O_6$:2HCl:$5H_2O$) C, H, N.

**17,17′-Dimethyl-6,6′,7,7′-tetrahydro-4,5:4′,5′-diepoxy-6,6′-(benzylimino)[7,7′-bimorphinan]-3,3′,14,14′-tetrol (1e).** 17,17′-Dimethyl-6,6′,7,7′-tetrahydro-4,5:4′,5′-diepoxy-6,6′-(imino)-[7,7′-bimorphinan]-3,3′,14,14′-tetrol (**1d**)[9] was treated as for **1b** above except MeOH/HBr replaces MeOH/HCl for the O-debenzylation. Yield 80%, MS (FAB): $m/z$ = 672 $(M + H)^+$, HRMS (FAB) $m/z$ 672.3063 $(M + H)^+$; $C_{41}H_{41}N_3O_6$ requires 671.2995, $R_f$ ($CH_2Cl_2$/MeOH/$NH_4OH$:110/10/1) 0.27 mp > 240 °C, Anal. ($C_{41}H_{41}N_3O_6$:2HCl:$4H_2O$) C, H, N.

**Acknowledgment.** This work was supported by NIDA Grant DA 07315.

**Supporting Information Available:** Full spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Schmidhammer, H. Opioid receptor antagonists. *Prog. Med. Chem.* **1998**, *35*, 83–132.
(2) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Bimorphinans as highly selective, potent κ opioid receptor antagonists. *J. Med. Chem.* **1987**, *30*, 238–239.
(3) Takemori, A. E.; Ho, B. Y.; Naeseth, J. S.; Portoghese, P. S. Norbinaltorphimine, a highly selective kappa-opioid antagonist in analgesia and receptor binding assays. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 255–258.
(4) Portoghese, P. S.; Sultana, M.; Takemori, A. E. Design of peptidomimetic delta opioid receptor antagonists using the message address concept. *J. Med. Chem.* **1990**, *33*, 1714–1720.
(5) Portoghese, P. S.; Nagase, H.; Takemori, A. E. Only one pharmacophore is required for the κ opioid antagonist selectivity of norbinaltorphimine. *J. Med. Chem.* **1988**, *31*, 1344–1347.
(6) Jones, R. M.; Portoghese, P. S. 5′-Guanidinonaltrindole, a highly selective and potent κ-opioid receptor antagonist. *Eur. J. Pharmacol.* **2000**, *396*, 49–52.
(7) Korlipara, V. L.; Takemori, A. E.; Portoghese, P. S. N–Benzylnaltrindoles as long-acting δ-opioid receptor antagonists. *J. Med. Chem.* **1994**, *37*, 1882–1885.
(8) Schmidhammer, H.; Smith, C. F. C. A simple and efficient method for the preparation of binaltorphimine and derivatives and determination of their κ opioid antagonist selectivity. *Helv. Chim. Acta* **1989**, *72*, 675–677.
(9) Portoghese, P. S.; Nagase, H.; Lipkowski, A. W.; Larson, D. L.; Takemori, A. E. Binaltorphimine-related bivalent ligands and their κ opioid receptor antagonist selectivity. *J. Med. Chem.* **1988**, *31*, 836–841.
(10) Broom, D. C.; Guo, L.; Coop, A.; Husbands, S. M.; Lewis, J. W.; Woods, J. H.; Traynor, J. R. BU48: A novel buprenorphine analogue that exhibits delta-opioid mediated convulsions but not delta-opioid mediated antinociception in mice. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 1195–1200.
(11) Traynor, J. R.; Nahorski, S. R. Modulation by mu-opioid agonists of guanosine-5′–O–(3-[S-35]thio)triphosphate binding to membranes from human neuroblastoma SH–SY5Y cells. *Mol. Pharmacol.* **1995**, *47*, 848–854.
(12) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. Binaltorphimine and nor-binaltorphimine, potent and selective κ-opioid receptor antagonists. *Life Sci.* **1987**, *40*, 1287–1289.
(13) Stevens, W. C.; Jones, R. M.; Subramanian, G.; Metzger, T. G.; Ferguson, D. M.; Portoghese, P. S. Potent and selective indolomorphinan antagonists of the kappa-opioid receptor. *J. Med. Chem.* **2000**, *43*, 2759–2769.
(14) Schutz, J.; Dersch, C. M.; Horel, R.; Spetea, M.; Koch, M.; Meditz, R.; Greiner, E.; Rothman, R. B.; Schmidhammer, H. Synthesis and biological evaluation of 14-alkoxymorphinans. 17. Highly d opioid receptor selective 14-alkoxy-substituted indolo- and benzofuromorphinans. *J. Med. Chem.* **2002**, *45*, 5378–5383.
(15) Portoghese, P. S.; Larson, D. L.; Sultana, M.; Takemori, A. E. Opioid agonist and antagonist activities of morphindoles related to naltrindole. *J. Med. Chem.* **1992**, *35*, 4325–4329.
(16) Broadbear, J. H.; Sumpter, T. L.; Burke, T. F.; Husbands, S. M.; Lewis, J. W.; Woods, J. H.; Traynor, J. R. Methocinnamox is a potent, long-lasting and selective antagonist of morphine-mediated antinociception in the mouse: Comparison with clocinnamox, β-FNA and β-chlornaltrexamine. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 933–940.
(17) Broadbear, J. H.; Negus, S. S.; Butelman, E. R.; de Costa, B. R.; Woods, J. H. Differential effects of systemically administered nor-binaltorphimine (norBNI) on κ-opioid agonists in the mouse writhing assay. *Psychopharmacology* **1994**, *115*, 311–319.
(18) Nieland, N. Investigations of derivatives of 14β-amino-7,8-dihydromorphinone. Thesis submitted to University of Bristol, UK, 1998.
(19) McLaughlin, J. P.; Hill, K. P.; Jiang, Q.; Sebastian, A.; Archer, S.; Bidlack, J. M. Nitrocinnamoyl and chlorocinnamoyl derivatives of dihydrocodeinone: *In vivo* and *in vitro* characterisation of μ-selective agonist and antagonist activity. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 304–311.

JM049172N